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RESEARCH**

*APPLICATION NUMBER:*

**21-229**

**ADMINISTRATIVE DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA # NDA 21-229 SUPPL # -----

Trade Name Prilosec OTC

Generic Name (omeprazole magnesium delayed-release tablets)

Applicant Name Proctor and Gamble  
HFD- 180

Approval Date 06/20/03

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES / x / NO / \_\_\_ /  
b) Is it an effectiveness supplement? YES / \_\_\_ / NO / x /

If yes, what type(SE1, SE2, etc.)? -----

- 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 / x / 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 /\_x\_/ NO /\_\_\_/

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

3

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

YES /\_x\_/ NO /\_\_\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_x\_/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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

YES /\_\_\_/ NO /\_x\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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.

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).

NDA # 19-810 Prilosec (omeprazole sodium)

NDA #

NDA #

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 #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /\_x\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /\_x\_/      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 9:

- (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 /\_x\_/      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 /\_x\_/

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 /\_x\_/

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:

Investigation #1, Study # 171

Investigation #2, Study # 183

Investigation #3, Study #

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 /\_x\_/

Investigation #2 YES /\_\_\_/ NO /\_x\_/

Investigation #3 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:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (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 /\_x\_/

Investigation #2                      YES /\_\_\_/                      NO /\_x\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (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"):

Investigation #\_\_, Study # 171

Investigation #\_\_, Study # 183

Investigation #\_\_, Study #

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 !  
! !  
IND # 54,307 YES / x / ! NO / \_\_\_ / Explain:  
! !  
! !  
! !  
! !  
Investigation #2 !  
! !  
IND # 54,307 YES / x / ! NO / \_\_\_ / Explain:  
! !  
! !  
! !  
! !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
! !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
! !  
! !  
! !  
! !  
Investigation #2 !  
! !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
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(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /\_x\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Melissa Furness  
Signature of Preparer

06/19/03  
Date

Title: Regulatory Project Manager

Dr. Robert Justice  
Signature of Office or Division Director

06/19/03  
Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

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Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Robert Justice  
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**PATENT INFORMATION  
PATENT CERTIFICATION**

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**ITEM 13  
PATENT INFORMATION**

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## Item 13

## Patent Information – Omeprazole Magnesium Tablets

The patent information for omeprazole magnesium tablets is provided in this section. Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2)(i).

| Patent No. | Patentee       | Expiry      | Patent Type                                     | Authorized Representative to Receive Notice of Patent Certification |
|------------|----------------|-------------|-------------------------------------------------|---------------------------------------------------------------------|
| 4738974    | AB Hässle      | 19 Apr 2005 | Drug Substance<br>Drug Product<br>Method of use | AstraZeneca LP                                                      |
| 5900424    | AstraZeneca AB | 4 May 2016  | Drug Substance<br>Method of use                 | AstraZeneca LP                                                      |
| 4786505    | AB Hässle      | 20 Apr 2007 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 4853230    | AB Hässle      | 20 Apr 2007 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5690960    | AstraZeneca AB | 25 Nov 2014 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5817338    | AstraZeneca AB | 6 Oct 2015  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5753265    | AstraZeneca AB | 7 Jun 2015  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 6403616    | AstraZeneca AB | 15 Nov 2019 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 6428810    | AstraZeneca AB | 3 Nov 2019  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |

**PATENT DECLARATION STATEMENT**

**DECLARATION**

The undersigned declares that U.S. Patent Numbers 4738974, 5900424, 4786505, 4853230, 5690960, 5817338, 5753265, 6403616 and 6428810 cover the formulation, composition and/or method of use of omeprazole magnesium tablets. This product is the subject of this application for which approval is being sought.

A handwritten signature in black ink, appearing to read "G. A. Gilbert", is written over a solid horizontal line.

**GEORGE A. GILBERT**

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**ITEM 14**  
**PATENT CERTIFICATION**

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**ITEM 14**  
**PATENT CERTIFICATION**

This application is not a 505(b)(2) application; therefore, the Patent Certification as described under 21 U.S.C. 355(b)(2) or (j)(2)(A) and 21 CFR 314.50(i) is not required.

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**ITEM 13  
PATENT INFORMATION**

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Item 13

**Patent Information – Omeprazole Magnesium Tablets**

The patent information for omeprazole magnesium tablets is provided in this section. Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2)(i).

| Patent No. | Patentee       | Expiry      | Patent Type                                     | Authorized Representative to Receive Notice of Patent Certification |
|------------|----------------|-------------|-------------------------------------------------|---------------------------------------------------------------------|
| 4255431    | AstraZeneca AB | Expired     | Drug Substance<br>Drug Product<br>Method of use | AstraZeneca LP                                                      |
| 4508905    | AB Hässle      | 2 Apr 2002  | Drug Substance                                  | AstraZeneca LP                                                      |
| 4738974    | AB Hässle      | 19 Apr 2005 | Drug Substance<br>Drug Product<br>Method of use | AstraZeneca LP                                                      |
| 4636499    | AB Hässle      | 30 May 2005 | Drug Substance                                  | AstraZeneca LP                                                      |
| 5900424    | AstraZeneca AB | 4 May 2016  | Drug Substance<br>Method of use                 | AstraZeneca LP                                                      |
| 4786505    | AB Hässle      | 20 Apr 2007 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 4853230    | AB Hässle      | 20 Apr 2007 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5690960    | AstraZeneca AB | 25 Nov 2014 | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5817338    | AstraZeneca AB | 6 Oct 2015  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5753265    | AstraZeneca AB | 7 Jun 2015  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |



**PATENT DECLARATION STATEMENT**

**DECLARATION**

The undersigned declares that U.S. Patent Numbers 4255431, 4738974, 5900424, 4786505, 4853230, 5690960, 5817338 and 5753265 cover the formulation, composition and/or method of use of omeprazole magnesium tablets. This product is the subject of this application for which approval is being sought.

A handwritten signature in cursive script, reading "Gary P. Horowitz", written over a horizontal line.

Gary P. Horowitz

Executive Director, Regulatory Affairs

AstraZeneca LP

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**ITEM 14  
PATENT CERTIFICATION**

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**ITEM 14  
PATENT CERTIFICATION**

This application is not a 505(b)(2) application; therefore, the Patent Certification as described under 21 U.S.C. 355(b)(2) or (j)(2)(A) and 21 CFR 314.50(i) is not required.

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**NDA 21-229**

**Submission Date: 23Mar00**

**ITEM 13**

**REVISED PATENT INFORMATION**

The patent information has been revised to include 1) all appropriate U.S Patent Numbers in the Declaration Statement listed in the table and 2) the authorized representative to receive notice of patent certification.

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**Item 13**

**Patent Information – Omeprazole Magnesium Tablets**

The patent information for omeprazole magnesium tablets is provided in this section. Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2)(i).

| Patent No. | Patentee  | Expiry                       | Patent Type                                     | Authorized Representative to Receive Notice of Patent Certification |
|------------|-----------|------------------------------|-------------------------------------------------|---------------------------------------------------------------------|
| 4255431    | Astra AB  | 5 Apr 1999<br>PTE 5 Apr 2001 | Drug Substance<br>Drug Product<br>Method of use | AstraZeneca LP                                                      |
| 4738974    | AB Hässle | 19 Apr 2005                  | Drug Substance<br>Drug Product<br>Method of use | AstraZeneca LP                                                      |
| 4636499    | AB Hässle | 30 May 2005                  | Drug Substance                                  | AstraZeneca LP                                                      |
| 5900424    | Astra AB  | 4 May 2016                   | Drug Substance<br>Method of use                 | AstraZeneca LP                                                      |
| 4786505    | AB Hässle | 20 Apr 2007                  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 4853230    | AB Hässle | 20 Apr 2007                  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5690960    | Astra AB  | 25 Nov 2014                  | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5817338    | Astra AB  | 6 Oct 2015                   | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |
| 5753265    | Astra AB  | 7 Jun 2015                   | Drug Product<br>Method of use                   | AstraZeneca LP                                                      |



**PATENT DECLARATION STATEMENT**

**DECLARATION**

The undersigned declares that U.S. Patent Numbers 4255431, 4738974, 5900424, 4786505, 4853230, 5690960, 5817338 and 5753265 cover the formulation, composition and/or method of use of omeprazole magnesium tablets. This product is the subject of this application for which approval is being sought.

A handwritten signature in cursive script, reading "Gary P. Horowitz", written over a horizontal line.

Gary P. Horowitz, Ph.D.

Executive Director, Regulatory Affairs

AstraZeneca LP

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**EXCLUSIVITY STATEMENT**

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**EXCLUSIVITY STATEMENT****Requesting Three Years Exclusivity**

As part of this New Drug Application, AstraZeneca LP (AZLP) is requesting three years exclusivity for the use of omeprazole magnesium delayed-release tablets (Prilosec OTC) for the over-the-counter (OTC) marketing for treatment of frequent heartburn.

Pursuant to 314.50(j) and 314.108(b)(4), support for exclusivity is based on the following:

1. The original NDA application dated 27 January 2000, the NDA Resubmission dated 12 February 2002 which are herein referenced, and this NDA resubmission contain the reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that are essential to the approval of this application. Contained in this NDA resubmission is a new Label Comprehension study (Study No. 22013) in which an iterative developmental process was used to select the best label that conveyed the labeling concepts required in the FDA Action Letter dated 8 August 2002.
2. The sponsor certifies that, to the best of our knowledge, each of the clinical investigations previously submitted in the original NDA application or submitted in this resubmission meets the definition of "new clinical investigation" set forth in 314.108(a).
3. The sponsor has thoroughly searched the literature for studies that are relevant to the conditions for which the applicant is seeking approval and, to the best of our knowledge, the list of published studies is accurate and complete and, in our opinion, the published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval.
4. AZLP is the sponsor and has assigned The Procter & Gamble Company (P&G) to be their agent for IND 54,307 (Serial No. 007) and NDA 21-229. Accordingly, the Form FDA 1571 lists P&G as the agent and AZLP as the sponsor.

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## **EXCLUSIVITY STATEMENT**

### **Requesting Three Years Exclusivity**

As part of this New Drug Application, AstraZeneca LP (AZLP) is requesting three years exclusivity for the use of omeprazole magnesium tablets (Prilosec 1™) for the over-the-counter (OTC) marketing for the treatment and prevention of heartburn.

Pursuant to 314.50(j) and 314.108(b)(4), support for exclusivity is based on the following:

1. The application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that are essential to the approval of this application.
2. The sponsor certifies that, to the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 314.108(a).
3. The sponsor has thoroughly searched the literature for studies that are relevant to the conditions for which the applicant is seeking approval and, to the best of our knowledge, the list of published studies is accurate and complete and, in our opinion, the published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval.
4. AZLP is the sponsor and has assigned P&G to be their agent for IND 54,307 (serial no. 007) and NDA 21-229. Accordingly, the 1571 forms list P&G as the agent and AZLP as the sponsor.

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ON ORIGINAL**

## REFERENCES RELEVANT TO TREATMENT OF HEARTBURN WITH OMEPRAZOLE

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- Dent J, Downton J, Heddl R et al. Effects of omeprazole on peptic oesophagitis and oesophageal motility and pH. *Scand J Gastroenterol* 1986; 21:181.
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**DEPARTMENT CERTIFICATION**

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**ITEM 16**  
**DEBARMENT CERTIFICATION**

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**ITEM 16  
DEBARMENT CERTIFICATION**

No new persons have been utilized in connection with this application since the 12 February 2002 Resubmission. Therefore, the Debarment Certification made in the 12-February 2002 remains valid, and is herein referenced.

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**DEBARMENT CERTIFICATION**

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, AstraZeneca LP did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

A handwritten signature in cursive script, reading "Gary P. Horowitz", written over a horizontal line.

Gary P. Horowitz, Ph.D.  
Executive Director, Regulatory Affairs

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## **Financial Disclosure**

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**ITEM 19**  
**FINANCIAL DISCLOSURE**

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**ITEM 19**  
**FINANCIAL DISCLOSURE**

This application does not contain any covered clinical studies as defined in 21 CFR Part 54. Therefore, a Financial Disclosure is not required.

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## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-229 Supplement Type (e.g. SE5):        Supplement Number:       

Stamp Date: 12/20/02 (current cycle) Action Date: 06/20/03

HFD-180 Trade and generic names/dosage form: Prilosec OTC (omeprazole magnesium delayed-release tablets)

Applicant: Proctor and Gamble Therapeutic Class:       

Indication(s) previously approved:       

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of frequent heartburn

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply:        Partial Waiver        Deferred        Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver: Please note that a waiver was not granted prior to the Pediatric Rule being challenged in court.

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: Children need to be seen by a physician and should not be self-medicated with this OTC product.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min        kg        mo.        yr.        Tanner Stage         
Max        kg        mo.        yr.        Tanner Stage       

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

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**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

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/s/

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Melissa Furness  
6/19/03 09:06:54 AM

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) [View Word Document](#)

**NDA Number:** 021229 **Trade Name:** PRILOSEC 1(OMEPRAZOLE MAGNESIUM)20MG TAB  
**Supplement Number:** 000 **Generic Name:** OMEPRAZOLE MAGNESIUM  
**Supplement Type:** N **Dosage Form:**  
**Regulatory Action:** OP **COMIS Indication:** TREATMENT/PREVENTION OF HEARTBURN  
**Action Date:** 1/27/00

Indication # 1 prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise

**Label Adequacy:** Inadequate for ALL pediatric age groups

**Formulation Needed:** NO NEW FORMULATION is needed

**Comments (if any):** This indication is not approvable. Sponsor requested a waiver for pediatric studies in children under the age of 12 with episodic heartburn. Since a new indication for "treatment of frequent heartburn" will be studied, the original waiver request is no longer pertinent. Information regarding the projected OTC usage for this new indication in 18 year old age group has been requested in the NA letter (11/27/00).

|  | <u>Lower Range</u> | <u>Upper Range</u> | <u>Status</u> | <u>Date</u> |
|--|--------------------|--------------------|---------------|-------------|
|  | 0 years            | 17 years           | Deferred      | 11/27/00    |

Indication # 2

**Label Adequacy:** Inadequate for ALL pediatric age groups

**Formulation Needed:** NO NEW FORMULATION is needed

**Comments (if any):** This indication is not approvable. Sponsor requested a waiver for pediatric studies in children under the age of 12 with episodic heartburn. Since a new indication for "treatment of frequent heartburn" will be studied, the original waiver request is no longer pertinent. Information regarding the projected OTC usage for this new indication in 18 year old age group has been requested in the NA letter (11/27/00).

|  | <u>Lower Range</u> | <u>Upper Range</u> | <u>Status</u> | <u>Date</u> |
|--|--------------------|--------------------|---------------|-------------|
|  |                    |                    |               |             |

Indication # 3

**Label Adequacy:** Inadequate for ALL pediatric age groups

**Formulation Needed:** NO NEW FORMULATION is needed

**Comments (if any):** This indication is not approvable. Sponsor requested a waiver for pediatric studies in children under the age of 12 with episodic heartburn. Since a new indication for "treatment of frequent heartburn" will be studied, the original waiver request is no longer pertinent. Information regarding the projected OTC usage for this new indication in 18 year old age group has been requested in the NA letter (11/27/00).

|  | <u>Lower Range</u> | <u>Upper Range</u> | <u>Status</u> | <u>Date</u> |
|--|--------------------|--------------------|---------------|-------------|
|  |                    |                    |               |             |

This page was last edited on 11/28/00

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 Signature

11/28/00  
 Date

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**MEMORANDUM**

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

**DATE:** June 26, 2003

**TO:** David Hilfiker, CPMS  
Division of Over-the-Counter Drug Products, HFD-560

**FROM:** Julieann DuBeau, CPMS  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**SUBJECT:** Transfer of NDA 21-229  
Prilosec OTC (omeprazole magnesium delayed-release tablets, 20mg)  
OTC use for treatment of frequent heartburn

In the line with the ORM policy of placing administrative responsibility of NDAs within the Division that reviews the principal clinical research activity of the drug, we are forwarding the attached NDA for your acceptance. If you do not concur, please include the reason as a signature comment. If you have any questions, call me at 301-443-8110.

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/s/

-----  
Julieann DuBeau  
6/26/03 01:17:22 PM

David Hilfiker  
6/26/03 02:06:30 PM

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8 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**Mason, Stephanie A**

---

**From:** Cothran, Helen  
**Sent:** Wednesday, December 01, 2004 9:40 AM  
**To:** Mason, Stephanie A  
**Subject:** RE: Prilosec OTC, NDA 21-229

Hi Stephanie,

I was told that the CP response issues from Office of Reg Policy (not OTC), but OTC cleared a draft response last week. It was then sent back to ORP, which sent it to GC. You can contact Cathy Jordan of ORP to check on the status. There are 2 letters relating to the Prilosec OTC issue, so when you check with Cathy, give her these two tracking numbers 5420 and 5842

Hope this helps.  
Helen

-----Original Message-----

**From:** Mason, Stephanie A  
**Sent:** Wednesday, December 01, 2004 8:37 AM  
**To:** Cothran, Helen  
**Subject:** RE: Prilosec OTC, NDA 21-229

Thanks. I just need to know because I am considering pulling Ganley's "internal" memo with comments regarding the petitioner's concerns, if OTC has not formally responded its comments to the petitioner.

Stef

-----Original Message-----

**From:** Cothran, Helen  
**Sent:** Tuesday, November 30, 2004 4:16 PM  
**To:** Mason, Stephanie A; Robinson, Mary S  
**Subject:** RE: Prilosec OTC, NDA 21-229

Steph,

I recall an Andryx petition some time ago, but I don't see it in our files as completed. I'll have to check with someone tomorrow.

Helen

-----Original Message-----

**From:** Mason, Stephanie A  
**Sent:** Tuesday, November 30, 2004 3:22 PM  
**To:** Robinson, Mary S  
**Cc:** Cothran, Helen  
**Subject:** Prilosec OTC, NDA 21-229



Hi Mary,

Hope you had a wonderful Thanksgiving. I know I did.

Anyway, can you tell me if the Citizen Petition (Andrx Pharm.) requesting that Prilosec OTC not be approved for OTC use has been responded to or if its still pending? I have a June 20, 2003 memorandum written by Dr. Ganley who states that the CP is still pending as of that date.

Thanks - Stephanie

**Division Director Memo**

|                                       |
|---------------------------------------|
| NDA #: 21-229                         |
| Drug Name: Prilosec OTC (Omeprazole)  |
| Sponsor: Proctor and Gamble           |
| Receipt Date: December 20, 2002       |
| PDUFA Date: June 20, 2003             |
| Type of Document: Resubmission to NDA |
| Date: June 20, 2003                   |

**Introduction**

This is the third review cycle for a new NDA for the use of Prilosec OTC for the treatment of heartburn. The sponsor has provided a significant amount of data in the previous review cycles. That information has been summarized in several previous memos. This memo was based on the reviews of Dr. Daiva Shetty, Dr. Karen Lechter and Dr. Atiar Rahman for data submitted during this review cycle. Dr. Justice<sup>1</sup> has written a separate memo that summarizes other issues related to the approval of this application.

**Recommendation**

1. The sponsor has submitted adequate information to support the approval of Prilosec OTC for the treatment of frequent heartburn. Study 22103 was an adequate well conducted study that addressed the consumer behavior issues listed in the approvable letter of August 8, 2002. After extensive internal discussion, the review team developed a label based on our review of the labeling comprehension study.
2. The sponsor requested the approval of a 14, 28 and 42 tablet package. We concur with these configurations based on previous discussions that each 14 tablet course is packaged separately to further emphasize that 14 tablets constitutes one course of therapy. They have also requested a 2 tablet sample pack. This can only be distributed to consumers that the sponsor pre-identified as having frequent heartburn. This should be noted in the approval letter.
3. The sponsor has requested that the term \_\_\_\_\_ be permitted on the principal display panel (PDP). We believe that this statement is misleading and would likely lead consumers to use the product outside of the conditions of use as specified on the OTC label. The approval letter should inform the sponsor that they should discuss with us the type of data and appropriate trial design that may support this language.
- 4.



**Background**

Dr. Shetty has nicely reviewed the history of the development program in her review. It will not be restated in this memo. Based on the discussion and recommendations of the advisory committee at the June 21, 2002 meeting, we agreed that the application was approvable and that an additional label comprehension study was needed to address consumer use issues. We did not feel that an actual use study, in lieu of a labeling comprehension study, was necessary because study 007 identified areas where consumer comprehension could be improved. The labeling concepts that needed improvement could be evaluated in a well-conducted label comprehension study<sup>2</sup>. In the approvable letter (August 8, 2002) for the second review cycle, the sponsor was asked to evaluate the following concepts in a labeling comprehension study:

- it is a 14 day treatment, is not intended for immediate treatment of or prevention of meal or beverage induced heartburn and it may take 1 - 2 days to work.
- which symptoms may be indicative of a more serious condition.
- it is not for use for more than 2 to 3 courses of treatment in one year at 3 to 4 month intervals.

<sup>1</sup> Director, Division of Gastrointestinal Drug Products

<sup>2</sup> Dr. Houn memo August 6, 2002

As part of this submission, the sponsor submitted the results of a labeling comprehension study (study 22103) to support the approval of Prilosec OTC.

### Label Comprehension Study 22103

With agency input, the sponsor designed and conducted study 22103. This study stratified consumers to one of four cohorts based on their literacy and frequency of heartburn. Literacy was determined using the Rapid Estimate of Adult Literacy (REALM) test. Low literate subjects were defined as having a score of 60 or less<sup>3</sup>. The study evaluated three different labels to establish which one would best convey the information to consumers. A total of 1842 subjects were included in the study. Table 1 shows the number of subjects in each cohort. Each subject was tested on one label so that approximately 150 subjects in each cohort viewed one of the three labels. The enrolled subjects were diverse with regard to demographic variables. Dr. Shetty and Dr. Lechter have provided extensive summaries of this study in their reviews.

Table 1. Number Of Subjects Enrolled in Each Cohort.

|                        |            | Literacy |     |
|------------------------|------------|----------|-----|
|                        |            | Normal   | Low |
| Frequency of heartburn | Frequent   | 456      | 480 |
|                        | Infrequent | 450      | 456 |

The results of the study are briefly outlined below.

#### *Use of the Product<sup>4</sup>*

- > 99% of the subjects understood that the product was for frequent heartburn
- approximately 8% of subjects thought it was also useful for immediate relief or prevention of meal induced heartburn (low literate group ( $\approx$  10%) was worse than the literate group ( $\approx$  5%))
- there was no difference between the three labels in comprehension for this issue
- when scenarios were used:
  - > 99% understood that the product was for frequent heartburn
  - approximately 85% were correct in understanding it was not for infrequent symptoms (this is driven by the low literate group (76 - 80%) vs literate group (92 - 95%))
  - approximately 80 - 85% were correct in understanding it was not for episodic symptoms (this is driven by the low literate group (74 - 80%) vs literate group (87 - 92%))
- One of the labels (label C) had in the Use section, "Not intended for immediate relief or prevention brought on by certain foods". This did not contribute to a better understanding of the use of the product. The understanding was quite high for all of the labels but the additional language did no improve the understanding in the low literate subjects.

#### *Self Selection<sup>5</sup>*

- > 99% of frequent heartburn sufferers selected correctly
- 79 - 84% of infrequent heartburn sufferers selected correctly. There was a difference between low literate (70 - 79%) and literate (87 - 93%) subjects.

#### *Warnings<sup>6</sup>*

- The comprehension for labeled warnings about other conditions or serious conditions was very good (greater than 93%).

#### *Directions for Use<sup>7</sup>*

- Based on scenarios:

<sup>3</sup> A score of 60 on the REALM test is approximately equal to a ninth grade reading level.

<sup>4</sup> From tables 9 - 14 of Dr. Shetty's review

<sup>5</sup> From table 15 of Dr. Shetty's review

<sup>6</sup> From table 17 of Dr. Shetty's review

<sup>7</sup> From table 20 - 21 of Dr. Shetty's review

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- 87 - 90 % understood the time of day to take the medication (literate ( $\approx$  94%) was better than low literate ( $\approx$  80 - 85%))
- greater than 95% understood the number of tablets to be used per day and the duration of therapy
- > 91% understood the time to reach full effect (this was evaluated in label C only).
- > 93% understood what to do if repeat episodes occurred
- for labels A and B, 90% understood how often to repeat the 14 day course (information on repeat courses was included in the directions; literate ( $\approx$  96%) was better than low literate ( $\approx$  85%))
- for label C, 78% understood how often to repeat the 14 day course (information on repeat courses was included in the Stop use and ask a doctor section; literate ( $\approx$  84%) was better than low literate ( $\approx$  72%))

In conclusion, the sponsor submitted a well conducted study. Some minor limitations in the way questions were designed as outlined by Dr. Lechter do not detract significantly from our ability to draw conclusions regarding the quality of the labeling. For most measures, comprehension was high. Low literate subjects not surprisingly had less comprehension for some measures. Even in these situations, their comprehension was in the 70 to 90% range. Any labeling deviations from the labels used in the studies were done to attempt to improve comprehension of low literate consumers.

### Labeling and Packaging

#### Drug Facts Labeling

Appendix 1 shows the Drug Facts label proposed by the sponsor during the second review cycle. The final Drug Facts label we recommend for approval is shown in Appendix 2. The major changes between the two labels are listed in Table 2.

**Table 2. Comparison of Major Changes to Label (Proposed label 2<sup>nd</sup> review cycle vs. Approved Label)**

| Proposed Label in 2 <sup>nd</sup> review cycle | Approved Label                                                                                                                                                                                                                                                            | Rationale                                                                                                                                                                                                                                                                                            |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                | <b>Use section:</b> <ul style="list-style-type: none"> <li>• treats frequent heartburn (occurs <u>2 or more</u> days a week)</li> <li>• not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect</li> </ul>                         | <ul style="list-style-type: none"> <li>• supported by results of study 22103</li> <li>• concepts combined into one bullet</li> <li>• minor changes to improve low literate comprehension</li> <li>• time to full effect included to apprise consumers of efficacy expectations.</li> </ul>           |
|                                                | Heartburn Warning removed                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>• information incorporated into Ask a doctor before use if you have section</li> <li>• supported by results of study 22103</li> </ul>                                                                                                                         |
|                                                | <b>Do not use if you have section:</b> <ul style="list-style-type: none"> <li>• trouble or pain swallowing food</li> <li>• vomiting with blood</li> <li>• bloody or black stools</li> </ul> These may be signs of a serious condition. See your doctor.                   | <ul style="list-style-type: none"> <li>• supported by results of study 22103</li> <li>• signs suggestive of a more serious condition recommended by the advisory committee</li> <li>• acid reducers removed as per August 8, 2002 approvable letter; see explanation following this table</li> </ul> |
|                                                | <b>Ask a doctor or pharmacist before use if you are taking section:</b> Add <ul style="list-style-type: none"> <li>• Digoxin (heart medication)</li> </ul>                                                                                                                | <ul style="list-style-type: none"> <li>• Narrow therapeutic index drug was important to add even though interaction is minimal</li> </ul>                                                                                                                                                            |
|                                                | <b>Directions section:</b> <ul style="list-style-type: none"> <li>• this product is to be used once a day (every 24 hours), every day for 14 days</li> <li>• it may take 1 to 4 days for full effect, although some people may get complete relief of symptoms</li> </ul> | <ul style="list-style-type: none"> <li>• supported by results of study 22103</li> <li>• based on information provided at the advisory committee on food interaction</li> <li>• repeat dose based on recommendation of advisory committee and results of study</li> </ul>                             |

| Proposed Label in 2 <sup>nd</sup> review cycle                       | Approved Label                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Rationale                                                                                                                                                                                                            |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| continues or returns, it could be a sign of a more serious condition | with 24 hours<br><b>14-Day Course of Treatment</b> <ul style="list-style-type: none"> <li>• swallow 1 tablet with a glass of water before eating in the morning</li> <li>• do not use for more than 14 days unless directed by your doctor</li> </ul> <b>Repeated 14-day Courses (if needed)</b> <ul style="list-style-type: none"> <li>• you may repeat a 14-day course every 4 months</li> <li>• do not take for more than 14 days or more often than every 4 months unless directed by a doctor</li> </ul> | 22103 <ul style="list-style-type: none"> <li>• time to full effect included to apprise consumers of efficacy expectations based on advisory committee recommendation; supported by results of study 22103</li> </ul> |

We considered what should be said in the labeling regarding concomitant use of other heartburn treatments and determined that the label should remain silent. Current prescription labeling permits the use of antacids and pharmacokinetic data gives conflicting results about an interaction. There is little clinical information about the interaction of an H2 blocker and a proton pump inhibitor. So, limiting the use of these drugs did not seem justified. If there is an interaction it is most likely to be on efficacy (we have no data in the safety database to suggest a safety issue), in that efficacy may be decreased. The consequence of this is that the product would not provide a benefit and the consumer would decide not to purchase it again. If symptoms recur and they follow labeled instructions, they should seek the advice of a doctor. We informed the sponsor of this decision in the August 8, 2002 approvable letter.

During the previous review cycles, there was a fair amount of deliberation regarding which drugs posed a significant interaction and should be included in the labeling. The final Prilosec label lists warfarin, antifungal medicines, diazepam and digoxin in the Ask a doctor or pharmacist before use if you are section of the Drug Facts label. We met with the sponsor on January 30, 2001 and decided that these drugs should be included on the label based on possible risks to the consumer.<sup>3</sup> At that time Clarithromycin was also considered for the list but later discounted because it causes elevations in omeprazole levels and does not impact on Clarithromycin levels. We did not believe that elevated levels of omeprazole related to this interaction with Clarithromycin was of significant clinical concern. Although the interaction with digoxin and warfarin is minimal, we decided to include them because of the narrow therapeutic index for both drugs.

*Package Insert*

The package insert provides additional information to the consumer that is consistent with Drug Facts labeling.

*Packaging*

The sponsor requested the approval of a 14, 28 and 42 tablet package. We concur with these configurations based on previous discussions that each 14 tablet course is packaged separately to further emphasize that 14 tablets constitutes one course of therapy. They have also requested a 2 tablet sample pack. This can only be distributed to consumers that the sponsor pre-identified as having frequent heartburn. This should be noted in the approval letter.

*\_\_\_\_\_ on Principal Display Panel*

The sponsor has requested that the term \_\_\_\_\_ be permitted on the principal display panel (PDP). We disagree and believe that this statement is misleading and would likely lead consumers to use the product outside of the conditions of use as specified on the OTC label. It is not clear how consumers view this term<sup>9</sup> and the sponsor has no data that indicates proper selection. The sponsor

<sup>3</sup> Meeting minutes of January 30, 2001 meeting between FDA and Proctor and Gamble

should provide supportive data that the ' \_\_\_\_\_ ' terminology would not mislead consumers. In light of the difficulty of this development program, especially related to self selection and appropriate use issues, it is surprising that the sponsor would want to include this on the package and not think it would impact on appropriate use in the OTC setting. The sponsor has withdrawn this request for now but has indicated they intend to submit it at a later date. The approval letter should encourage the sponsor to seek guidance on the type of data and appropriate trial design that may support this language.

/S/

Charles J. Ganley, M.D.

cc: orig.

- HFD-560 /shay /cothran/robinson/shetty/leonard segal/rosebraugh
- HFD-180/justice/korvick/gallo torres/furness
- HFD-105/bull/harvey/rumble
- HFD-103/houn/beitz/

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✓ § 552(b)(5) Draft Labeling

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Division Director Summary Review of a New Drug Application

NDA: 21-229

Drug: Prilosec OTC (omeprazole magnesium) 20 mg Delayed-Release Tablets

Applicant: The Procter and Gamble Company (agent for AstraZeneca LP)

Date: June 19, 2003

Original Submission

This new drug application for Prilosec OTC (previously named Prilosec 1) was originally submitted on January 27, 2000. The application included six efficacy studies, 5 actual use studies, and 1 label comprehension study in support of the OTC use of Prilosec 1 in three indications: 1) relief of heartburn, acid indigestion, and sour stomach, 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise, and 3) prevention of heartburn for 24 hours. The efficacy data were reviewed by Dr. Lawrence Goldkind on November 11, 2000. Dr. Goldkind concluded that Prilosec 1 should not be approved as proposed by the sponsor. However, he concluded that "studies 171 and 183 represent replicated evidence of efficacy of OM for the prevention of HB over a 14-day period." Both trials were multicenter, randomized, double-blind, placebo-controlled studies to investigate the safety and efficacy of omeprazole magnesium, 10 mg qd and 20 mg qd in preventing heartburn. The five-week study had three phases: a single-blind placebo run-in period of one week, a double-blind randomized treatment period of two weeks, and a single-blind placebo follow-up period of two weeks. To be eligible subjects had to have heartburn on at least two days per week over the past month and the heartburn must respond to some degree to antacids or OTC H<sub>2</sub>-receptor antagonists. To be eligible for randomization subjects must have had heartburn on at least two days during the run-in period. Subjects completed a diary designed to collect information on maximum heartburn severity, nocturnal heartburn, and antacid consumption over the previous 24 hours (Gelusil use was permitted). The primary efficacy endpoint was no heartburn over 24 hours and the primary evaluation period was between the first and second daily doses. The results for no heartburn over 24 hours on days 1 and 14 are shown below.

| No Heartburn Over 24 Hours on Day 1 |                 |                 |                 |
|-------------------------------------|-----------------|-----------------|-----------------|
|                                     | Ome-Mg 20 mg    | Ome-Mg 10 mg    | Placebo         |
| Study 171 <sup>a,b,c</sup>          | 49.7% (260/523) | 41.5% (215/518) | 32.6% (169/519) |
| Study 183 <sup>d,e,f</sup>          | 46.8% (245/524) | 45.2% (235/520) | 32.1% (167/520) |

<sup>a</sup> 20 mg vs. placebo p<0.001

<sup>b</sup> 10 mg vs. placebo p=0.003

<sup>c</sup> 20 mg vs. 10 mg p=0.008

<sup>d</sup> 10 mg vs. placebo p<0.001

<sup>f</sup> 20 mg vs. 10 mg p=0.572

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| No Heartburn Over 24 Hours on Day 14 |              |              |         |
|--------------------------------------|--------------|--------------|---------|
|                                      | Ome-Mg 20 mg | Ome-Mg 10 mg | Placebo |
| Study 171 <sup>a,b</sup>             | 69.7%        | 71.7%        | 42.7%   |
| Study 183 <sup>c,d,e</sup>           | 73.0%        | 66.4%        | 32.0%   |

<sup>a</sup> 20 mg vs. placebo p<0.05

<sup>b</sup> 10 mg vs. placebo p<0.05

<sup>c</sup> 20 mg vs. placebo p<0.05

<sup>d</sup> 10 mg vs. placebo p<0.05

<sup>e</sup> 20 mg vs. 10 mg p<0.05

Studies 171 and 183 demonstrated that omeprazole magnesium is effective in increasing the proportion of patients with no heartburn over 24 hours and that the effectiveness increases from Day 1 to Day 14. In study 171, on Day 1 the dose of 20 mg was superior to 10 mg in providing control of heartburn. However, there was no difference between the doses on Day 14. In study 183 there was no difference in control of heartburn between the doses on Day 1. However, on Day 14 the dose of 20 mg dose was superior to 10 mg.

The safety review was completed by Dr. Mark Avigan on January 20, 2000. Rare adverse events of concern included liver toxicity, toxic epidermal necrolysis and Stevens-Johnson Syndrome, bone marrow suppression, including agranulocytosis, urticaria/skin rashes, and anaphylaxis/angioedema. Other concerns included pregnancy category C status, pediatric use, the potential for GI adenocarcinomas, acid rebound, and drug/drug interactions. Dr Avigan recommended non-approval.

Dr. Avigan's review also discussed the metabolism of omeprazole by CYP2C19 and the fact that 3% of Caucasians and 15% of Asians are slow metabolizers. He noted that the consequences of the resultant longer half-lives is that the slow metabolizers "manifest a higher 24 hour median intragastric pH and longer intervals per 24 hours in which intragastric pH is greater than 4." The applicant argued that the elimination half-life in slow metabolizers would still be shorter than the dosing interval and that accumulation would be negligible. In the CLINICAL PHARMACOLOGY section of the package insert for prescription Prilosec it states that "In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered." However, the safety of a 14-day course of omeprazole 20 mg in slow metabolizers is supported by 14 years of postmarketing experience (see below) and the safety of doses of up to 120 mg t.i.d. (360 mg/day) in patients with Zollinger-Ellison syndrome who have received treatment continuously for periods of more than 5 years. In addition, overdosages with doses up to 2400 mg have been reported with only transient symptoms and no serious clinical outcomes.

The applicant's Integrated Summary of Safety included an analysis of safety data from the OTC clinical trials. The database includes 11,299 subjects: 5,040 on omeprazole magnesium 20 mg, 3,139 on omeprazole magnesium 10 mg, and 3,120 on placebo. The

most common adverse events for both 20 mg and 10 mg were headache, infection, and diarrhea. No SAE reported by subjects receiving 20 mg was considered to be possibly or probably related to study drug. One subject receiving 10 mg had angioedema/serum sickness classified as probably drug-related. There were no laboratory findings of concern in any treatment group. The postmarketing surveillance database identified diarrhea, headache, nausea, abdominal pain, and rash as the most frequent adverse events. The applicant concluded that there was "no indication of an increased risk of hepatic dysfunction, cardiac conduction disturbances, visual abnormalities, TEN, SJS, acute pancreatitis, anaphylaxis, angioedema, agranulocytosis, or gastrointestinal cancer with omeprazole."

An OPDRA Postmarketing Safety Review was completed on August 14, 2000. The overall conclusion was that "Given the number of years that omeprazole has been on the market (11) and its extensive use ( \_\_\_\_\_ prescriptions<sup>1</sup>), AERS report data suggest that the frequency of adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, unreporting must be considered."

The pharmacology review of September 12, 2000 by Dr. Timothy Robinson recommended non-approval. Concerns included genotoxicity both *in vitro* and *in vivo*, genotoxicity in reproductive toxicology studies in both rats and rabbits, tumorigenicity in rats, and an incomplete carcinogenicity study in a second species.

These issues were discussed at a joint meeting of the Gastrointestinal Drugs and Nonprescription Drugs Advisory Committees on October 20, 2000. The committee felt that adequate information was not available to support the proposed indications and approval was not recommended. However, the committee voted 7 to 6 with 1 abstention that the treatment of common heartburn as well as GERD was an acceptable OTC indication. In addition, the committee stated that the safety profile of Prilosec 1 was acceptable for OTC use. The committee voted 7 to 5 with 2 abstentions that the safety concerns for OTC marketing for short term or intermittent use, including anaphylaxis/angioedema/urticaria, liver toxicity, white blood cell disorders and severe skin reactions could be addressed by labeling. The committee also voted 8 to 5 with 1 abstention that other safety concerns (masking of serious disease, potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity, rebound hyperacidity, and hypergastrinemia) could be addressed. The committee concluded that none of these issues would prevent approval. In discussions with OTC it was determined that rare adverse events of uncertain relationship to a drug are not included in OTC labeling.

A not approvable letter was issued on November 27, 2000. The basis for the action was that "the efficacy, appropriate dose and duration of therapy, and use of Prilosec 1 in the OTC setting have not been adequately established. Further, the ability of the consumer to appropriately self-select and to use Prilosec 1 safely and effectively in the OTC setting has not been demonstrated. Thus, a favorable benefit/risk profile has not been established for OTC use." The letter stated that the data from studies 171 and 183 do support the efficacy of either 10 mg or 20 mg per day for up to 10 days in the treatment

<sup>1</sup> Confidential IMS data. Not for release.

of individuals with chronic heartburn. However, additional label comprehension studies were needed and should be followed by actual use studies when suitable labeling has been identified. The letter went on to state that the appropriate dose and duration of therapy for this indication requires further consideration. In addition, "the implications of use of OTC omeprazole by consumers who may need long-term treatment for GERD and/or erosive esophagitis must be considered." It was noted that in performing additional label comprehension and actual use studies, it should be demonstrated that consumers understand that the product will not acutely relieve symptoms. Regarding the potential for drug-drug interactions, the ability of consumers to avoid concomitant use with interacting drugs without the intervention of a physician must be demonstrated. Safety issues to be addressed included the absence of adequate safety information in individuals under 18, potential risks to the fetus, the need to establish that consumers will not use the drug for extended periods of time without contacting a health care provider, and the clinical importance of gastric acid rebound following discontinuation. Finally, the name Prilosec 1 was found to be unacceptable.

#### First Resubmission

On February 12, 2002 the applicant submitted a complete response to the November 27, 2000 action letter. The application requested approval of the indication for the prevention of frequent heartburn (2 or more days a week) and consisted of 2 actual use and one label comprehension studies. Another joint advisory committee meeting was held on June 12, 2002. The committee voted 16 to 2 that it is acceptable that some patients with GERD +/- erosive esophagitis would self-treat with OTC medication. The committee voted 15 to 3 that the applicant had not demonstrated that consumers could self-select for use of Prilosec 1. The committee also voted 17 to 1 in favor of a 14-day course of treatment and 16 to 2 that the sponsor provided sufficient information to support the approval of Prilosec 1 for the prevention of frequent heartburn. The committee recommended that Prilosec 1 should not be used for more than 2-3 courses/year. Finally the committee recommended extensive labeling revisions and retesting for comprehension.

On August 8, 2002 an approvable letter was issued for the indication of 14-day treatment of frequent heartburn. The applicant was asked to revise the labeling and to conduct a new label comprehension study that would evaluate the revised labeling. Concepts on the carton to be evaluated included differentiation from antacids and H<sub>2</sub> receptor antagonists (e.g., omeprazole is not intended for the immediate treatment of heartburn) and that the drug may take 1 to 2 days of use to work. Specific concepts for "Heartburn Warning" were recommended. Revisions to the following sections were recommended: *Do not use, Ask a doctor before use if you have, When using this product, Ask a doctor or pharmacist before use if you are taking, Stop use and ask a doctor if,* and *Directions*. The letter stated that the package insert was promotional and contained misleading statements and that the entire insert must be revised to present factual and educational information for consumers. In addition, the proposed package insert must include detailed information about the critical points identified in the carton label. The letter further stated that the name Prilosec 1 was not acceptable, that new may be used on labels

and labeling for a period not to exceed 6 months, that "Delayed-Release" should be added before "Tablets," and that directions should be provided in all of the labeling to swallow the tablet whole and not chew or crush in food.

An update of the ODS Postmarketing Safety Review was completed on June 14, 2002. The review concluded that "During the time period since the previous consult (April 1, 2000 through April 25, 2002), omeprazole continues to be used extensively in the U.S. ( — prescriptions from April 1, 2000 through March 31, 2002<sup>2</sup>) with an average length of therapy of 6 months and AERS report data suggest that the frequency of serious adverse events associated with omeprazole continues to be low; however, with any evaluation of spontaneous reports, under-reporting must be considered." Another ODS Postmarketing Safety Review of cases of anaphylaxis was completed on July 10, 2002. The conclusion was that "Omeprazole is used extensively in the U.S. ( — prescriptions from January 1, 1990 through March 31, 2002<sup>3</sup>), AERS report data suggest that the frequency of anaphylaxis associated with omeprazole use is low."

### Second Resubmission

A complete response to the approvable letter was submitted on December 20, 2002. The submission contains a label comprehension study, proposed OTC labeling, and a safety update. The review by Dr. Daiva Shetty of OTC was completed on April 23, 2003. Dr. Shetty concluded that label B is well understood and would be approvable with suggested modifications. In addition, the safety data "did not present any safety signals that would preclude Prilosec from OTC marketing."

The Labeling Comprehension Study was also reviewed by Dr. Karen Lechter of DSRCS on May 2, 2003. She concluded that most scores were very high, regardless of the label and that scores may have been inflated due to methodologic inadequacies. She noted that in many cases Label B scored numerically higher than Labels A and C by a few points. She recommended development of clearer language or formatting to increase understanding that users are not to repeat courses of treatment more often than every four months since Low Literate groups had low comprehension of this concept. In addition, she recommended that the information about repeated use in the "Stop use and ask a doctor" section be kept in this section, as well as in the directions section, as it is in Label B. She also recommended retention of the "recipe" format for dosing that separates the first course of treatment from later ones as is used in Labels A and B. Additional suggestions included modifying the message about episodic use so that it will be clear in the Low Literate subgroup, clarifying the language about the time of day to take the medicine, and retaining the language that it may take one to two days to reach full effect.

### Other Reviews

The chemistry review of April 16, 2003 concluded that from the standpoint of CMC this application can be approved.

<sup>2</sup> Confidential IMS data. Not for release.

<sup>3</sup> Confidential IMS data. Not for release.

The Clinical Pharmacology and Biopharmaceutics Review was completed on November 13, 2000. The review concluded that the "To-Be-Marketed (TBM) omeprazole tablets were shown to be similar, but not bioequivalent, to the marketed prescription capsules. However, additional PK and clinical studies were submitted to the current application in support of the safety and efficacy of omeprazole magnesium tablets." The review noted that "food significantly affects the bioavailability of omeprazole 20 mg MUPS tablets. Prilosec 1 20 mg MUPS tablets should be administered one hour before food intake since it was administered as such during the clinical trials." Food increases the AUC of the tablet by 20% while decreasing the  $C_{max}$  by 34%. However, in the pivotal studies (171 and 183) the drug was to be taken before breakfast. In addition, the prescription drug labeling states that Prilosec is to be given before meals. In drug-drug interaction studies, clarithromycin increased the AUC and  $C_{max}$  for omeprazole by 100% and 60%, respectively. However, omeprazole 40 mg is approved for use in combination with clarithromycin for the indication *H. pylori* eradication. In drug interaction studies with diazepam, omeprazole exhibited dose-dependent inhibition of diazepam metabolism. The diazepam interaction is mentioned in the labeling.

The Medical Team Leader Review dated May 31, 2003 by Dr. Hugo Gallo-Torres recommended approval.

#### Major Labeling Issues

The applicant agreed to make the following changes to the labeling submitted on December 20, 2002.

- Delete \_\_\_\_\_
- Use "new" for only the first 6 months of marketing
- Clarify that "Prilosec OTC may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours"
- Emphasize that the drug should not be chewed, crushed, or crushed in food because it decreases how well Prilosec works
- Remove the statement that Prilosec " \_\_\_\_\_ " from the section on How Prilosec Works for Your Frequent Heartburn

The final draft labeling is acceptable.

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Recommended Regulatory Action

The application should be approved.

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Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal and Coagulation  
Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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**Labeling Review**  
**Division of OTC Drug Products**  
**HFD-560**

|                                                   |                                                  |
|---------------------------------------------------|--------------------------------------------------|
| <b>NDA #:</b> 21-229                              | <b>Sponsor:</b> Procter and Gamble Company       |
| <b>Drug Product:</b> Omeprazole Magnesium Tablets | <b># of Stock Keeping Units in Submission:</b> 5 |
| <b>Submission Dates:</b> June 16, 2003            | <b>Review Date:</b> June 17, 2003                |
| <b>Type of Submission:</b> NDA                    | <b>Reviewer:</b> Mary S. Robinson, HFD-560       |

**Background**

In response to the agency's June 16, 2003, facsimiles (dated June 14, 2003), Procter and Gamble submitted proposed draft labeling. Full color printed labeling of the 14, 28, and 42 count cartons, configuration of outer cartons containing 28 and 42 count, configuration of plastic overlay for 42 count package, package insert, blister card, and trial sample size are included in this submission. This is a review of the proposed labeling contained in this submission. (See attachment.)

**Stock Keeping Unit:** (describe unit) 14, 28, and 42 count cartons and outer cartons containing 28 and 42 count

**Information Included in the submission follows:**

| <b>Content of Submission</b>                                                                                                                                        | <b>Yes</b> | <b>No</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|
| A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s);                           | ✓          |           |
| A table of contents or index                                                                                                                                        | ✓          |           |
| The most recent approved labeling                                                                                                                                   | ✓          |           |
| A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product. | ✓          |           |
| Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 13293.                                                                        | ✓          |           |

Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review:            Yes

**Reviewer Comments and Recommendations**

1. Principal Display Panel. The sponsor states that the statement "NEW!" will be deleted after the first 6 months of OTC marketing.
2. Carton back panel, 14, 28, and 42 count packages, back panel trial sample size label, package insert.  
     The "Active ingredient" statement is revised to read: Omeprazole magnesium delayed-release tablet 20.6 mg (equivalent to 20 mg omeprazole)
3. The "Drug Facts" title is reduced in size from 14 point to 10 point on the carton back panel, 14, 28, 42 count packages, and the back panel trial size.

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NDA # 21-229

The revisions in 2 and 3 above are acceptable. This submission can be approved.

[ ISI ] 6/17/03

Mary S. Robinson, M.S.  
Regulatory Review Chemist, HFD-560

for [ ISI ] R.Ph. 6/17/03  
Helen Cothran,  
Team Leader, HFD-560

cc: HFD-560: CGanley/CRosebraugh/ASegal/DShetty/DKeravich/HCothran/MRobinson  
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\_\_\_\_\_ § 552(b)(5) Draft Labeling

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CENTER FOR DRUG EVALUATION AND RESEARCH  
FOOD AND DRUG ADMINISTRATION

**FACSIMILE TRANSMISSION RECORD**

DATE: 06/14/03

FROM: Daniel P. Keravich, RPh., MSc., MBA.  
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2248                      FAX: 301-827-2316 or  
301-827-2315

TO: Linda Jones  
Proctor and Gamble

FAX #: 513-622-1996\_No. Of Pages (including cover) 2

\*\*\*\*\*  
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**Message:**

Please find the review division labeling comments regarding revised draft labeling submitted on June 12, 2002, for Prilosec OTC®, NDA 21-229, submitted December 20, 2002.

The attached labeling comments are provided for content only and do not reflect the requirements listed under CFR 201.66 for labeling under 21CFR Part 201 for Over-the-Counter Human Drugs; Labeling requirements, Final Rule.

If you have any questions, please contact Daniel P. Keravich, R.Ph., M.Sc., M.B.A., Regulatory Project Manager, at 301-827-2248.

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1. Principal Display Panel. Delete the statement "NEW!" after the first 6 months of OTC marketing.
2. Carton back panel, 14, 28, and 42 count packages, back panel trial sample size label, package insert.
  - Revise the "Active ingredient" statement to read: Omeprazole magnesium delayed-release tablet 20.6 mg (equivalent to 20 mg omeprazole)

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/s/

-----  
Daniel Keravich  
6/16/03 12:03:55 PM  
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# THE PROCTER AND GAMBLE COMPANY

## HEALTH CARE RESEARCH CENTER

Shipping Address:  
8700 Mason Montgomery Road  
Mason, OH 45040-9462

Mailing Address:  
P.O. Box 8006  
Mason, OH 45040-8006

### FACSIMILE COVER SHEET

TO: Melissa Furnes

Company: FDA

Phone: 301-827-7450

Fax: 301-443-9285

FROM: LINDA JONES

Company: The Procter & Gamble Company

Phone: 513-622-3176

Fax: 513-622-~~3397~~ 1896

Date: 6/13/03

Pages including cover page: 30

#### COMMENTS:

Hi melissa,  
I wanted to provide a fax of the revised draft labeling submission filed yesterday. Two desk copies of this submission were sent to your attention. The electronic pdf version + original hard copy were sent to Dr Justice's attention.  
Thanks for everything you are doing for US!!!  
Best Regards, Linda

#### IMPORTANT INFORMATION CONFIDENTIALITY NOTICE

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# Procter & Gamble

The Procter & Gamble Company  
Health Care Research Center  
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

12 June 2003

Robert L. Justice, M.D., M.S., Director  
Division of Gastrointestinal and Coagulation Drug Products  
Food and Drug Administration  
HFD-180, Room 6B-45  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Justice:

**Re: NDA 21-229: Prilosec OTC™  
(omeprazole magnesium delayed-release tablets)  
Submission of Revised Draft Labeling**

Reference is made to the 20 December 2002 NDA Resubmission in response to the Agency's 8 August 2002 Approvable Letter. Reference is also made to the Agency's 21 May, 29 May, 4 June, and 11 June 2003 facsimiles in response to our 20 December 2002 Resubmission, and our 22 May and 30 May 2003 facsimiles.

The Agency's comments have been incorporated. Revised draft labeling is provided in Item 2 - Labeling.

In addition to changes referenced above, three minor labeling changes have been made. These three changes and the reason for each change are as follows:

**1. Drug Facts**

a. Change in listing of active ingredient per 21 CFR 201.66

*Active ingredient (in each tablet)*

"Omeprazole magnesium delayed-release tablet 20.6 mg  
(equivalent to 20 mg omeprazole)"

was changed to:

---

This was done to be in compliance to 21 CFR 201.66.

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*Procter & Gamble*

NDA 21-229: PRILOSEC OTC™  
 Submission of Revised Draft Labeling – Item 2.0  
 Page 2

**2. Package Insert**

a. Change in active ingredient statement

The active ingredient statement under the Prilosec OTC logo heading was changed from:

“Omeprazole magnesium delayed-release tablets 20.6 mg (equivalent to omeprazole 20 mg) Acid reducer”

to:

\_\_\_\_\_

This change was made to be consistent with the active ingredient statement in Drug Facts.

b. Package Insert – Change in Wording of Last Section

[ \_\_\_\_\_ ]

was changed to read:

[ \_\_\_\_\_ ]

This change was made to be consistent with the carton labeling. Further, we did not want consumers to believe they could learn information other than that communicated in the FDA-approved labeling for Prilosec OTC.

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*Procter&Gamble*

NDA 21-229: PRILOSEC OTC™  
Submission of Revised Draft Labeling – Item 2.0  
Page 3

Following is a description of the electronic media and paper review copies of this submission:

- 1) File size: ~11 MB
- 2) Number of CDs: 1 (for archival)
- 3) Word Version (MS Word 97) of updated labeling provided on diskette.
- 4) Review Aid/Desk Copies of Labeling (1 – Clinical Review Aid, 2 – GI Desk Copies, 2 – OTC Desk Copies).
- 5) This electronic filing is virus free (Norton AntiVirus v5.02.00).

Please do not hesitate to contact myself at (513) 622-1673 or Ms. Linda Jones at (513) 622-3176 should you have any questions.

Sincerely,



Barbara A. Kochanowski, Ph.D.  
Associate Director, Product Safety and  
Regulatory Affairs, Personal Health Care

Cc: Ms. Melissa Furness, Regulatory Project Manager, Division of Gastrointestinal and  
Coagulation Drug Products  
Mr. Dan Keravich, Regulatory Project Manager, Division of Over-the-Counter Drug  
products

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This application contains the following items: (Check all that apply)

|                                     |                                                                                                                            |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | 1. Index                                                                                                                   |
| <input checked="" type="checkbox"/> | 2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/>            | 3. Summary (21 CFR 314.50 (c))                                                                                             |
| <input type="checkbox"/>            | 4. Chemistry section                                                                                                       |
|                                     | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)                           |
|                                     | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)                                      |
|                                     | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601 Electronic Format 2)                             |
| <input type="checkbox"/>            | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)                              |
| <input type="checkbox"/>            | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)                           |
| <input type="checkbox"/>            | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))                                                                      |
| <input type="checkbox"/>            | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)                                                        |
| <input type="checkbox"/>            | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)                                                |
| <input type="checkbox"/>            | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)                                                         |
| <input type="checkbox"/>            | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)                                                     |
| <input type="checkbox"/>            | 12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)                                                           |
| <input type="checkbox"/>            | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))                                      |
| <input type="checkbox"/>            | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))          |
| <input type="checkbox"/>            | 15. Establishment description (21 CFR Part 600, if applicable)                                                             |
| <input type="checkbox"/>            | 16. Debarment certification (FD&C Act 306 (k)(1))                                                                          |
| <input type="checkbox"/>            | 17. Field copy certification (21 CFR 314.50 (k) (3))                                                                       |
| <input type="checkbox"/>            | 18. User Fee Cover Sheet (Form FDA 3397)                                                                                   |
| <input type="checkbox"/>            | 19. Financial Information (21 CFR Part 54)                                                                                 |
| <input type="checkbox"/>            | 20. OTHER (Specify) (Exclusivity Statement and Pediatric Deferral)                                                         |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210, 211, or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 990 and/or 909.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

|                                                                                                 |                                                                                                                     |                                  |
|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------|
| SIGNATURE OF RESPONSIBILITY OFFICIAL OR AGENT<br><i>Barbara A. Kochanowski</i>                  | TYPED NAME AND TITLE<br>Barbara A. Kochanowski, Ph.D., Associate Director,<br>Product Safety and Regulatory Affairs | DATE<br>6/12/03                  |
| ADDRESS (Street, City, State, and Zip Code)<br>8700 Mason-Montgomery Road, Mason, OH 45040-9462 |                                                                                                                     | Telephone Number<br>513-622-1673 |

Public reporting burden for this collection of information is estimated to average 24 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 burden to:

Department of Health and Human Services  
Food and Drug Administration  
CBER, HPM-69  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
12420 Parklawn Dr., Room 3046  
Rockville, MD 20852

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**NDA 21-229: PRILOSEC OTC™**  
**(omeprazole magnesium delayed-release tablets)**

**Item 2.0: Revised Draft Labeling (12 June 2003)**

**Table of Contents**

This section provides revised draft labeling based on the Agency's feedback of 21 May, 29 May, 4 June, and 11 June 2003 facsimiles.

| <b>Description</b>                                                             | <b>Review Copy<br/>Page Number of<br/>this Submission</b> | <b>Archive Copy File Name</b> |
|--------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------|
| <b>Introduction</b>                                                            | 1 of 23                                                   | N21229_12Jun03\labeling.pdf   |
| <b>Appendix 1 – Carton and<br/>Package Labeling Text</b>                       | 3 of 23                                                   | N21229_12Jun03\labeling.pdf   |
| <b>Appendix 2</b>                                                              | 8 of 23                                                   | N21229_12Jun03\labeling.pdf   |
| <b>2.1 14-Count Cartons</b>                                                    | 9 of 23                                                   | N21229_12Jun03\labeling.pdf   |
| <b>2.2 28 and 42 Count<br/>  Cartons</b>                                       | 13 of 23                                                  | N21229_12Jun03\labeling.pdf   |
| <b>2.3 Configuration of<br/>  Plastic Overlay for<br/>  42-Count Package</b>   | 17 of 23                                                  | N21229_12Jun03\labeling.pdf   |
| <b>2.4 Package Insert</b>                                                      | 18 of 23                                                  | N21229_12Jun03\labeling.pdf   |
| <b>2.5 Blister Card</b>                                                        | 20 of 23                                                  | N21229_12Jun03\labeling.pdf   |
| <b>2.6 Trial Sample Size</b>                                                   | 21 of 23                                                  | N21229_12Jun03\labeling.pdf   |
| <b>Appendix 3 – Drug Facts<br/>Labeling with Formatting<br/>Specifications</b> | 23 of 23                                                  | N21229_12Jun03\labeling.pdf   |

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**NDA 21-229: PRILOSEC OTC™**  
**(omeprazole magnesium delayed-release tablets)**  
**Item 2.0: Revised Draft Labeling (12 June 2003)**

**INTRODUCTION**

On 21 May 2003, the FDA provided feedback on our proposed labeling in the 20 December 2002 Resubmission. The Agency also provided input on our proposed alternate language on several labeling components (29 May, 4 June, and 11 June 2003 facsimiles). This section contains revised labeling based on the cumulative FDA feedback.

The Agency's comments have been incorporated. Three minor labeling changes were also made. These changes and the basis for each modification are as follows:

**1. Drug Facts**

a. Change in listing of active ingredient per 21 CFR 201.66

*Active ingredient (in each tablet)*

"Omeprazole magnesium delayed-release tablet 20.6 mg  
(equivalent to 20 mg omeprazole)"

was changed to:

---

This was done to be in compliance to 21 CFR 201.66.

**2. Package Insert**

a. Change in active ingredient statement

The active ingredient statement under the Prilosec OTC logo heading was changed from:

"Omeprazole magnesium delayed-release tablets 20.6 mg (equivalent to omeprazole 20 mg) Acid reducer"

to:

---

This change was made to be consistent with the active ingredient statement in Drug Facts.

1

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b. Change in Wording of Last Section

[ \_\_\_\_\_ ]

was changed to read:

[ \_\_\_\_\_ ]

This change was made to be consistent with the carton labeling. Further, we did not want consumers to believe they could learn information other than that communicated in the FDA-approved labeling for Prilosec OTC.

Following is revised draft labeling per the Agency's feedback.

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21 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**Labeling Review**  
**Division of OTC Drug Products**  
**HFD-560**

|                                                   |                                                  |
|---------------------------------------------------|--------------------------------------------------|
| <b>NDA #: 21-229</b>                              | <b>Sponsor: Procter and Gamble Company</b>       |
| <b>Drug Product: Omeprazole Magnesium Tablets</b> | <b># of Stock Keeping Units in Submission: 5</b> |
| <b>Submission Dates: June 12, 2003</b>            | <b>Review Date: June 13, 2003</b>                |
| <b>Type of Submission: NDA</b>                    | <b>Reviewer: Mary S. Robinson, HFD-560</b>       |

**Background**

In response to the agency's May 21, 29, June 4, 11, 2003, facsimiles, Procter and Gamble submitted proposed draft labeling. Printed labeling of the 14, 28, and 42 count cartons, configuration of outer cartons containing 28 and 42 count, configuration of plastic overlay for 42 count package, package insert, blister card, and trial sample size are included in this submission. This is a review of the proposed labeling contained in this submission. (See attachment.)

**Stock Keeping Unit: (describe unit) 14, 28, and 42 count cartons and outer cartons containing 28 and 42 count**

**Information Included in the submission follows:**

| <b>Content of Submission</b>                                                                                                                                        | <b>Yes</b> | <b>No</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|
| A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s);                           | ✓          |           |
| A table of contents or index                                                                                                                                        | ✓          |           |
| The most recent approved labeling                                                                                                                                   | ✓          |           |
| A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product. | ✓          |           |
| Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 13293.                                                                        | ✓          |           |

Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review:           **Yes**

**Reviewer Comments and Recommendations**

The following maybe conveyed to the sponsor:

1. Principal Display Panel. Delete the statement "NEW!" after the first 6 months of OTC marketing.
2. Carton back panel, 14, 28, and 42 count packages, back panel trial sample size label, package insert.

Revise the "Active ingredient" statement to read: Omeprazole magnesium delayed-release tablet 20.6 mg (equivalent to 20 mg omeprazole)

3. The Graphic specifications for the labeling are acceptable.

The revision in 2, above needs to be made before approval.

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NDA # 21-229

[            ISI ]

] 6/13/03

Mary S. Robinson, M.S.  
Regulatory Review Chemist, HFD-560

[            ISI ]

] 6/13/03

Helen Cothran,  
Team Leader, HFD-560

cc: HFD-560: CGanley/CRosebraugh/ASegal/DShetty/DKeravich/HCothran/MRobinson  
HFD-180

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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Marina Chang  
6/16/03 02:56:47 PM  
INTERDISCIPLINARY

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**FACSIMILE TRANSMISSION RECORD**

DATE: 06/11/03  
FROM: Daniel P. Keravich, RPh., MSc., MBA.  
Division of OTC Drug Products, HFD-560  
PHONE: 301-827-2248 FAX: 301-827-2316 or  
301-827-2315  
TO: Linda Jones  
Proctor and Gamble

FAX #: 513-622-1996\_No. Of Pages (including cover) 2

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**Message:**

Please find the review division labeling comments regarding your proposal to the agency's fax dated June 4, 2003, for Prilosec OTC®, NDA 21-229, submitted December 20, 2002.

The attached labeling comments are provided for content only and do not reflect the requirements listed under CFR 201.66 for labeling under 21CFR Part 201 for Over-the-Counter Human Drugs; Labeling requirements, Final Rule.

If you have any questions, please contact Daniel P. Keravich, R.Ph., M.Sc., M.B.A., Regulatory Project Manager, at 301-827-2248.

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With regard to your proposal on the package insert under A. What to Expect When Using Prilosec OTC, \_\_\_\_\_

After additional internal discussion regarding the use of the word \_\_\_\_\_ instead of \_\_\_\_\_, we believe the use of the word \_\_\_\_\_ is more reflective of the data. We have the following comments.

1. Over the first 24 hours after the first dose, the difference between placebo and Prilosec in the percentage of subjects with no heartburn ranged from 14.9% and 17.1%. So, the relative effect of Prilosec during the first day really did not effect many of the subjects in the study.
2. The intent of the statement is to alert consumers that it may take several days to obtain complete relief of symptoms. The statement is reflective of what occurred in the clinical study and is being generalized to the population of consumers. The word \_\_\_\_\_ accomplishes this.

The following statement should be used.

[ \_\_\_\_\_ ]

With regards to your proposal under **Directions** in the Drug Facts Carton, the following statement should be used.

- it may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours

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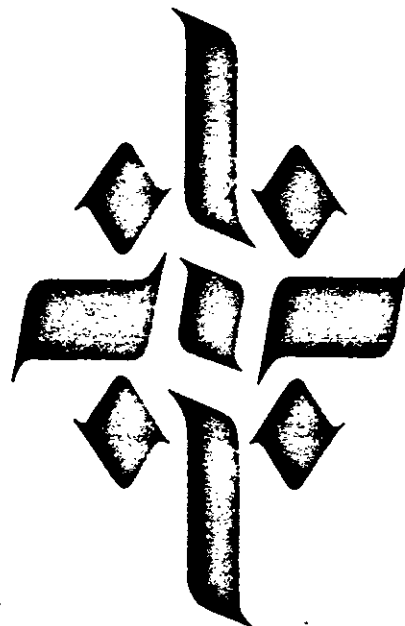
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Daniel Keravich  
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FOOD AND DRUG ADMINISTRATION  
DIVISION OF OTC DRUG PRODUCTS  
OFFICE OF DRUG EVALUATION V  
CENTER FOR DRUG EVALUATION & RESEARCH  
5600 FISHERS LANE, HFD-560  
ROCKVILLE, MD 20857-001  
301-827-2222 (phone)  
301-827-2315 (fax)  
DATE 6-4-03



TO: Linda Jones

PHONE: 513-622-3176

FAX: 513-622-1996

         PGS. (FAX + COVER)

FROM: WALT ELLENBERG

MESSAGE Linda

I have attach a copy of Dr. Kochanowski's May 30, 2003  
Letter to Dr. Ganby. PLEASE note That this letter  
has been revised and now includes our current  
comments.

Let me know if you have questions.

Thanks [K/]

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Date: 5/30/03

From: Barbara Kochanowski, Ph.D.  
Associate Director, Regulatory Affairs

Phone: 513-622-1673

Dear Dr. Ganley,

We appreciate the Agency's feedback on our proposed labeling (facsimile dated 5/21/03) and on our alternative language on several components (facsimile dated 5/29/03). We have accepted almost all of the Agency's input to the label. Regarding the package insert and Drug Facts labeling below, we are proposing three minor modifications to ensure consumers are appropriately educated about the product's benefits and use. Our proposed modifications are as follows:

2

**1. Package Insert**

**A. What to Expect When Using Prilosec OTC**

**FDA's Proposal (5/29/03):** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Sponsor's Proposal:** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Sponsor's Position:** We believe changing \_\_\_\_\_ (which could have multiple meanings) to "\_\_\_\_\_" (which means a large number but not necessarily a majority) best describes the product's benefits and is a more accurate representation of the clinical data.

**Agency Response (6/4/03):**

**The sentence in question should read:**

**Prilosec OTC may take 1 to 4 days for full effect, although some people get complete relief of symptoms after 24 hours.**

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**Drug Facts - Carton**

We are proposing the following modifications for consistency between the package insert and the Drug Facts carton labeling:

***Directions***

A. We propose adding "every 24 hours" at the end of the second bullet in the Directions section so that this section is the same as the directions in the package insert. Therefore, the second bullet would read:

- this product is to be used once a day (every 24 hours), every day for 14 days

**Agency Response (6/4/03):**

**This is acceptable.**

B. We are also proposing adding the following bullet to the Directions section immediately following the second bullet (e.g., "this product is to be used ...")

- \_\_\_\_\_

**Agency Response (6/4/03):**

**This phrase alone loses its context when the complete phrase is not included. You can include the complete phrase from the package insert in the Directions section.**

- **it may take 1 to 4 days for full effect, although some people get complete relief of symptoms after 24 hours**

As stated above, this additional bullet helps educate the consumer on the product's benefit, what to expect when using the product, and ensures consistency between the package insert and Drug Facts labeling.

We look forward to hearing from you on the acceptability of our proposals.

Barbara Kochanowski, Ph.D.  
Associate Director, Personal Health Care  
(513) 622-1673

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Walter J. Ellenberg  
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Date: 5/30/03

From: Barbara Kochanowski, Ph.D.  
Associate Director, Regulatory Affairs

Phone: 513-622-1673

Dear Dr. Ganley,

We appreciate the Agency's feedback on our proposed labeling (facsimile dated 5/21/03) and on our alternative language on several components (facsimile dated 5/29/03). We have accepted almost all of the Agency's input to the label. Regarding the package insert and Drug Facts labeling below, we are proposing three minor modifications to ensure consumers are appropriately educated about the product's benefits and use. Our proposed modifications are as follows:

**1. Package Insert**

**A. What to Expect When Using Prilosec OTC**

FDA's Proposal (5/29/03):

[ \_\_\_\_\_ ]

Sponsor's Proposal:

[ \_\_\_\_\_ ]

Sponsor's Position: We believe changing \_\_\_\_\_ (which could have multiple meanings) to \_\_\_\_\_ (which means a large number but not necessarily a majority) best describes the product's benefits and is a more accurate representation of the clinical data.

**2. Drug Facts - Carton**

We are proposing the following modifications for consistency between the package insert and the Drug Facts carton labeling:

***Directions***

A. We propose adding "every 24 hours" at the end of the second bullet in the Directions section so that this section is the same as the directions in the package insert.

Therefore, the second bullet would read:

- this product is to be used once a day (every 24 hours), every day for 14 days

B. We are also proposing adding the following bullet to the Directions section immediately following the second bullet (e.g., "this product is to be used ...")

- \_\_\_\_\_

As stated above, this additional bullet helps educate the consumer on the product's benefit, what to expect when using the product, and ensures consistency between the package insert and Drug Facts labeling.

We look forward to hearing from you on the acceptability of our proposals.

Barbara Kochanowski, Ph.D.  
Associate Director, Personal Health Care  
(513) 622-1673

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH  
FOOD AND DRUG ADMINISTRATION

**FACSIMILE TRANSMISSION RECORD**

DATE: 05/29/03

FROM: Daniel P. Keravich, RPh., MSc., MBA.  
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2248 FAX: 301-827-2316 or  
301-827-2315

TO: Linda Jones  
Proctor and Gamble

FAX #: 513-622-3573\_No. Of Pages (including cover) 7

\*\*\*\*\*  
**This document is intended for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any view, disclosure, copying, or other action based on the content of this communication is NOT authorized.**  
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**Message:**

Please find the review divisions' responses to your two faxes dated May 22, 2002 (attached) in which you had requested points seeking clarification and proposed alternative language based on information listed on the agency's fax dated May 21, 2002. You are requested to submit revised draft labeling as soon as possible.

If you have any questions, please contact Daniel P. Keravich, R.Ph., M.Sc., M.B.A., Regulatory Project Manager, at 301-827-2248.

**APPEARS THIS WAY  
ON ORIGINAL**

## Points Seeking Clarification Responses

### I. P&G Comments on Blister Card

- 1) It has been our intention to provide the expiration date and lot number on the blister. It will be printed once along the bottom of the card. Is this sufficient?
- 2) Regarding the inclusion of the net content statement, could you please clarify?

We have read the referenced section of the act and are still unclear since the information on our blister card appears to be in-line with other acid reducer blister card units.

### FDA Response

- 1) Please indicate the exact locations for the lot number and the expiration date on the blister card. Suggest you utilize a fictitious number and date such as : LN:XXXXXX and Exp. XX/XX/XXXX on the mockup.
- 2) A net quantity statement of either one or 1 is required on each blister pouch label. The (s) on tablets should also be removed. Please refer to 201.62(A)  
Suggested format: one omeprazole delayed-release tablet *or*  
1 omeprazole delayed-release tablet

### II. Drug Facts

FDA's Proposal: "Not intended for immediate relief of heartburn: this drug may take 1 to 4 days for full effect"

Sponsor's Concern: This statement will imply to consumers that Prilosec OTC doesn't work until 4 days after starting therapy. In addition, "full effect" could be interpreted by consumers to mean the drug is done working and no further dosing is needed. Finally, this statement will be excerpted by competitors in advertising and used as evidence from FDA that Prilosec OTC doesn't work until day 4 of treatment. We are fully committed to properly communicating that this drug is not intended for immediate relief of heartburn, that the efficacy of the drug increases over time and that nearly 50% of consumers get complete relief and over 80% of consumers get partial symptom relief after the first dose.

Sponsor's Proposal: \_\_\_\_\_

### FDA RESPONSE

The agency does not agree. The proposal by the sponsor is actually more confusing. It suggests that in all cases you get an increase in the effect over four days. The two divisions appreciate the possible marketing claims that competitors will make. If Proctor and Gamble believes that a competitor uses the phrases out of context, the divisions will work with the FTC to determine whether the advertising is misleading.

**BEST POSSIBLE COPY**

## Package Insert

### A. What to Expect When Using Prilosec OTC

#### FDA's Proposal:

[ \_\_\_\_\_ ]

Sponsor's Concern: As stated above.

#### Sponsor's Proposal

[ \_\_\_\_\_ ]

Rationale: Our clinical studies and the pharmacology of the drug provide substantial evidence that consumers will experience a benefit on day 1. We believe the additional statement (Many consumers will experience benefit on day 1) provides needed balanced perspective to the "1-4 day" concept proposed by FDA. Finally, we believe it is important to clarify the reason for once per day by clearly communicating that each dose lasts for a 24 hr. period.

#### FDA RESPONSE

Please see the FDA response to drug facts labeling proposal listed under II. The labeling could be revised to the following:

"Prilosec OTC is a different type of medicine from antacids and other acid reducers. Prilosec OTC may take 1 to 4 days for full effect, although some consumers may get complete relief of symptoms after the first dose. Make sure you take the entire 14 days of dosing to treat your frequent heartburn."

### B. How Prilosec OTC Works for Your Frequent Heartburn

#### FDA's Proposal:

Prilosec OTC works differently from other OTC heartburn products such as antacids and other acid reducers. Prilosec OTC stops acid production at the source – the acid pump that produces stomach acid.

Sponsor's Concern: Dosing information for OTC medicines is normally communicated to consumers in units of "hours". Additionally, to consumers a "day" is often interpreted as meaning "during the daytime". For example, Pepcid AC advertising speaks of "all day (i.e. 12 hrs.) or all night relief".

Sponsor's Proposal: We recommend revising the last sentence to read "Prilosec OTC is to be used once a day (every 24 hours), every day for 14 days."

APPEARS THIS WAY  
ON ORIGINAL

"Every 24 hours" was added to enhance consumer understanding of the concept 1 pill per day. Other heartburn medications can be taken up to several times a day. We believe this additional wording will reinforce 1 pill a day usage behavior.

**FDA RESPONSE**

The agency does agree. Please revise the last sentence to read "Prilosec OTC is to be used once a day (every 24 hours), every day for 14 days."

**III. Principal Display Panel (PDP) - \_\_\_\_\_**

**FDA's Proposal:** Delete ' \_\_\_\_\_ ' from PDP

**Sponsor's Concern:** In this category, as in most other categories, previous Rx to OTC switches have occurred at 1/2 prescription strength. Consumers may think they need to take 2 doses to get a prescription dose if that was their desire.

**Sponsor's Proposal:** Add \_\_\_\_\_ to PDP

We believe retaining \_\_\_\_\_ on the PDP will facilitate consumer understanding that Prilosec OTC is at 20 mg. \_\_\_\_\_

**FDA RESPONSE**

The agency does not agree. The proposed labeling may be acceptable if this was a complete switch. We are concerned that patients taking the prescription product for other indications may take this product because of the \_\_\_\_\_ labeling. This product is not intended for prescription product indications. The December 12, 2002 minutes do not reflect an actual agreement or alignment on this issue.

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ON ORIGINAL

Attachments- Fax From Sponsor

Fax #1

Date: 5/22/03

From: Linda C. Jones  
The Procter & Gamble Co.  
Barbara Kochanowski, Ph.D.  
Associate Director, Regulatory Affairs

Phone: 513-622-3176 (L. Jones)  
513-622-1673 (B. Kochanowski)

Dan,

Barb and I are providing this fax to facilitate our discussion later this morning. We greatly appreciate your willingness to dialog with us on a couple of the Agency's points in the 5/21/03 facsimile. As we mentioned in our message, we are okay with the majority of the comments and are looking forward to final approval.

Points seeking clarification

Blister Card

- 3) It has been our intention to provide the expiration date and lot number on the blister. It will be printed once along the bottom of the card. Is this sufficient?
- 4) Regarding the inclusion of the net content statement, could you please clarify?  
We have read the referenced section of the act and are still unclear since the information on our blister card appears to be in-line with other acid reducer blister card units.

PDP

- 1) The Agency requested we delete "\_\_\_\_\_". We would appreciate understanding the Agency's position on this request. This was discussed at the 12 December 2002 meeting and we thought we were aligned on this topic.  
As mentioned during the meeting, we believe the inclusion of "\_\_\_\_\_ " will help alleviate consumer confusion in the marketplace, especially since the H2s were switched at half prescription strength. There also appears to be some precedent here.  
Is the Agency open to alternative language (e.g. \_\_\_\_\_) ?

Package Insert

- 1) The Agency removed the sentence "\_\_\_\_\_".  
Could you share insights as to the Agency's thinking of this? This wording was included in the PI to help convey appropriate product usage (1 pill a day every 24 hours) and the product's benefit.
- 2) The Agency revised the "\_\_\_\_\_ day statement to "1 - 4" days. We believe we have the same goal as the FDA; that is, to ensure appropriate consumer usage. We are concerned consumers may think the product doesn't really work until maybe 4 days after starting therapy. Reality is that the drug does work in the majority of consumers shortly after initiating therapy. Would the Agency be open to alternative language, while still communicating the 1-4 day message?

Thanks Dan for your attention to our questions! Looking forward to speaking to you soon. Linda

Attachments- Fax From Sponsor

Fax #2

Date: 5/22/03

From: Linda C. Jones

The Procter & Gamble Co.

Barbara Kochanowski, Ph.D.

Associate Director, Regulatory Affairs

Phone: 513-622-3176 (L. Jones)

513-622-1673 (B. Kochanowski)

Dan,

As we discussed earlier today, there are 4 items for which we are proposing alternative language. These items and our proposed alternatives are as follows:

1. Drug Facts

FDA's Proposal: "Not intended for immediate relief of heartburn: this drug may take 1 to 4 days for full effect"

Sponsor's Concern: This statement will imply to consumers that Prilosec OTC doesn't work until 4 days after starting therapy. In addition, "full effect" could be interpreted by consumers to mean the drug is done working and no further dosing is needed. Finally, this statement will be excerpted by competitors in advertising and used as evidence from FDA that Prilosec OTC doesn't work until day 4 of treatment. We are fully committed to properly communicating that this drug is not intended for immediate relief of heartburn, that the efficacy of the drug increases over time and that nearly 50% of consumers get complete relief and over 80% of consumers get partial symptom relief after the first dose.

Sponsor's Proposal: \_\_\_\_\_

2. Package Insert

What to Expect When Using Prilosec OTC

FDA's Proposal:

[ \_\_\_\_\_ ]

Sponsor's Concern: As stated above in item #1.

Sponsor's Proposal

Prilosec OTC is a different type of medicine from antacids and other acid reducers. Prilosec OTC's effect increases over the first 1 - 4 days of use. Many consumers will experience benefit on day one. Each dose lasts up to 24 hours. Make sure you take the entire 14 days of dosing to treat your frequent heartburn.

Rationale: Our clinical studies and the pharmacology of the drug provide substantial evidence that consumers will experience a benefit on day 1. We believe the additional statement (Many consumers will experience benefit on day 1) provides needed balanced perspective to the "1-4 day" concept proposed by FDA. Finally, we believe it is important to clarify the reason for once per day by clearly communicating that each dose lasts for a 24 hr. period.

### 3. How Prilosec OTC Works for Your Frequent Heartburn

FDA's Proposal:

[ \_\_\_\_\_ ]

Sponsor's Concern: Dosing information for OTC medicines is normally communicated to consumers in units of "hours". Additionally, to consumers a "day" is often interpreted as meaning "during the daytime". For example, Pepcid AC advertising speaks of "all day (i.e. 12 hrs.) or all night relief".

Sponsor's Proposal: We recommend revising the last sentence to read "Prilosec OTC is to be used once a day (every 24 hours), every day for 14 days."

"Every 24 hours" was added to enhance consumer understanding of the concept 1 pill per day. Other heartburn medications can be taken up to several times a day. We believe this additional wording will reinforce 1 pill a day usage behavior.

### 4. Principal Display Panel (PDP) - \_\_\_\_\_

FDA's Proposal: Delete " \_\_\_\_\_ " from PDP

Sponsor's Concern: In this category, as in most other categories, previous Rx to OTC switches have occurred at 1/2 prescription strength. Consumers may think they need to take 2 doses to get a prescription dose if that was their desire.

Sponsor's Proposal: Add " \_\_\_\_\_ " to PDP

We believe retaining " \_\_\_\_\_ " on the PDP will facilitate consumer understanding that Prilosec OTC is at 20 mg \_\_\_\_\_

We look forward to hearing from you on the acceptability of our proposals.

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/s/

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Daniel Keravich  
5/29/03 01:23:08 PM  
CSO

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ON ORIGINAL

**Furness, Melissa**

---

**From:** Keravich, Daniel  
**Sent:** Tuesday, May 27, 2003 8:55 AM  
**To:** Cothran, Helen; Rosebraugh, Curtis  
**Cc:** Furness, Melissa  
**Subject:** FW: Request for FAXES-

-----Original Message-----

**From:** jones.lc@pg.com [mailto:jones.lc@pg.com]  
**Sent:** Friday, May 23, 2003 12:35 PM  
**To:** Keravich, Daniel  
**Subject:** RE: Request for FAXES

Thanks Dan. \_\_\_\_\_ a. Our marketing people felt the same way, but our counter parts indicated this was the recommended wording.

Thanks for arranging your internal meeting. We'll stay on standby late in the day with the hopes of hearing something from you yet on Tuesday so that we can continue to move forward on submitting revised labeling that week.

Linda

Internet Mail Message  
Received from host: ocswall2.fda.gov  
[198.77.181.8]

**From:** "Keravich, Daniel" <KeravichD@cder.fda.gov> on 05/23/2003 01:04 PM GMT

**"Keravich, Daniel"** **To:** Linda Jones-LC/PGI  
<KeravichD@cder.fda.gov> **Cc:** "Furness, Melissa"

<FurnessM@cder.fda.gov>

**Subject:** RE: Request for FAXES

05/23/2003 09:04 AM

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1   Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**Furness, Melissa**

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**From:** Keravich, Daniel  
**Sent:** Friday, May 23, 2003 9:22 AM  
**To:** Furness, Melissa; Korvick, Joyce A; Justice, Robert  
**Cc:** Ganley, Charles J; Cothran, Helen; Robinson, Mary S  
**Subject:** FW: Request for FAXES



Microsoft Word Microsoft Word

4

4

Bob, Joyce, & Melissa

Lots of progress on Prilosec labeling. See attached faxes! One document (21KB) is a fax for clarification and the other (27KB) is a fax for their proposals for alternative language - per my request.

I have set up a 330pm to 4pm meeting on Tuesday to discuss their alternative language requests. I have provided feedback on the Blister card clarification points for LN and exp dating. We are contacting CDER compliance to see if P&G takes the (s) off of tablets on the blister pack label, if the tablet (singular) will comply with the net quantity statement since a tablet is self evident in net quantity. I will be able to tell you more on Tuesday.

Thanks

Dan

-----Original Message-----

**From:** jones.lc@pg.com [mailto:jones.lc@pg.com]  
**Sent:** Friday, May 23, 2003 8:44 AM  
**To:** keravichd@cdcr.fda.gov  
**Cc:** kochanowski.ba@pg.com  
**Subject:** Request for FAXES

Hi Dan,

As per your request, attached are the two faxes we sent you yesterday.

Also, could you look into why \_\_\_\_\_  
was  
removed from labeling?

Thanks so much for all your help!

Linda

(See attached file: N2122922May03fax2labelingresponse.doc) (See attached file: N2122922May03faxlabelingresponse.doc)

Date: 5/22/03

From: Linda C. Jones  
The Procter & Gamble Co.  
Barbara Kočanowski, Ph.D.  
Associate Director, Regulatory Affairs  
Phone: 513-622-3176 (L. Jones)  
513-622-1673 (B. Kočanowski)

Facts  
Received from  
the firm 5/23/03  
RE: Clarification  
of and  
proposals for alternate  
language in labeling

Dan,

As we discussed earlier today, there are 4 items for which we are proposing alternative language. These items and our proposed alternatives are as follows:

### 1. Drug Facts

FDA's Proposal: "Not intended for immediate relief of heartburn: this drug may take 1 to 4 days for full effect"

Sponsor's Concern: This statement will imply to consumers that Prilosec OTC doesn't work until 4 days after starting therapy. In addition, "full effect" could be interpreted by consumers to mean the drug is done working and no further dosing is needed. Finally, this statement will be excerpted by competitors in advertising and used as evidence from FDA that Prilosec OTC doesn't work until day 4 of treatment. We are fully committed to properly communicating that this drug is not intended for immediate relief of heartburn, that the efficacy of the drug increases over time and that nearly 50% of consumers get complete relief and over 80% of consumers get partial symptom relief after the first dose.

Sponsor's Proposal: \_\_\_\_\_

### 2. Package Insert

#### **What to Expect When Using Prilosec OTC**

FDA's Proposal:

\_\_\_\_\_ ]

Sponsor's Concern: As stated above in item #1.

#### Sponsor's Proposal

Prilosec OTC is a different type of medicine from antacids and other acid reducers. Prilosec OTC's effect increases over the first 1 - 4 days of use. Many consumers will experience benefit on day one. Each dose lasts up to 24 hours. Make sure you take the entire 14 days of dosing to treat your frequent heartburn.

Rationale: Our clinical studies and the pharmacology of the drug provide substantial evidence that consumers will experience a benefit on day 1. We believe the additional

statement (Many consumers will experience benefit on day 1) provides needed balanced perspective to the "1-4 day" concept proposed by FDA. Finally, we believe it is important to clarify the reason for once per day by clearly communicating that each dose lasts for a 24 hr. period.

### 3. How Prilosec OTC Works for Your Frequent Heartburn

#### FDA's Proposal:

Sponsor's Concern: Dosing information for OTC medicines is normally communicated to consumers in units of "hours". Additionally, to consumers a "day" is often interpreted as meaning "during the daytime". For example, Pepcid AC advertising speaks of "all day (i.e. 12 hrs.) or all night relief".

Sponsor's Proposal: We recommend revising the last sentence to read "Prilosec OTC is to be used once a day (every 24 hours), every day for 14 days."

"Every 24 hours" was added to enhance consumer understanding of the concept 1 pill per day. Other heartburn medications can be taken up to several times a day. We believe this additional wording will reinforce 1 pill a day usage behavior.

### 4. Principal Display Panel (PDP) -

FDA's Proposal: Delete ' \_\_\_\_\_ ' from PDP

Sponsor's Concern: In this category, as in most other categories, previous Rx to OTC switches have occurred at 1/2 prescription strength. Consumers may think they need to take 2 doses to get a prescription dose if that was their desire.

Sponsor's Proposal: Add ' \_\_\_\_\_ ' to PDP

We believe retaining ' \_\_\_\_\_ ' on the PDP will facilitate consumer understanding that Prilosec OTC is at 20 mg, \_\_\_\_\_

We look forward to hearing from you on the acceptability of our proposals.

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ON ORIGINAL

Date: 5/22/03

From: Linda C. Jones  
The Procter & Gamble Co.  
Barbara Kochanowski, Ph.D.  
Associate Director, Regulatory Affairs

Phone: 513-622-3176 (L. Jones)  
513-622-1673 (B. Kochanowski)

Dan,

Barb and I are providing this fax to facilitate our discussion later this morning. We greatly appreciate your willingness to dialog with us on a couple of the Agency's points in the 5/21/03 facsimile. As we mentioned in our message, we are okay with the majority of the comments and are looking forward to final approval.

**Points seeking clarification**

**Blister Card**

- 1) It has been our intention to provide the expiration date and lot number on the blister. It will be printed **once** along the bottom of the card. Is this sufficient?
- 2) Regarding the inclusion of the net content statement, could you please clarify? We have read the referenced section of the act and are still unclear since the information on our blister card appears to be in-line with other acid reducer blister card units.

**PDP**

- 1) The Agency requested we delete \_\_\_\_\_ We would appreciate understanding the Agency's position on this request. This was discussed at the 12 December 2002 meeting and we thought we were aligned on this topic.

As mentioned during the meeting, we believe the inclusion of '\_\_\_\_\_  
\_\_\_\_\_' will help alleviate consumer confusion in the marketplace, especially since the H2s were switched at half prescription strength. There also appears to be some precedent here.

Is the Agency open to alternative language ' \_\_\_\_\_ ,?'

**Package Insert**

- 1) The Agency removed the sentence " \_\_\_\_\_  
\_\_\_\_\_". Could you share insights as to the Agency's thinking of this? This wording was included in the PI to help convey appropriate product usage (1 pill a day every 24 hours) and the product's benefit.
- 2) The Agency revised the ' \_\_\_\_\_ day statement to "1 - 4" days. We believe we have the same goal as the FDA; that is, to ensure appropriate consumer usage. We are concerned consumers may think the product doesn't really work until maybe 4 days after starting therapy. Reality is that the drug does work in the majority of consumers shortly after initiating therapy. Would the Agency be open to alternative language, while still communicating the 1-4 day message?

Thanks Dan for your attention to our questions! Looking forward to speaking to you soon.  
Linda

CENTER FOR DRUG EVALUATION AND RESEARCH  
FOOD AND DRUG ADMINISTRATION

**FACSIMILE TRANSMISSION RECORD**

DATE: 05/21/03

FROM: Daniel P. Keravich, RPh., MSc., MBA.  
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2248 FAX: 301-827-2316 or  
301-827-2315

TO: Linda Jones  
Proctor and Gamble

FAX #: 513-622-1996\_No. Of Pages (including cover) 8

\*\*\*\*\*  
**This document is intended for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any view, disclosure, copying, or other action based on the content of this communication is NOT authorized.**  
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**Message:**

Please find the review divisions' mock-ups regarding the Drug Facts and package insert of the labeling for Prilosec OTC®, NDA 21-229 submitted December 20, 2002. We have also included the reviewers' comments concerning the principal display panel, trial size and blister pouch. You are requested to submit revised draft labeling as soon as possible.

Please note that we have also attached a brief explanation for the changes in the Use section of the Drug Facts and **What to Expect When Using Prilosec OTC** section of the package insert regarding the number of days for full effect statement.

The attached labeling comments are provided for content only and do not reflect the requirements listed under CFR 201.66 for labeling under 21CFR Part 201 for Over-the-Counter Human Drugs; Labeling requirements, Final Rule.

If you have any questions, please contact Daniel P. Keravich, R.Ph., M.Sc., M.B.A., Regulatory Project Manager, at 301-827-2248.

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

## Reviewers Additional Comments - NDA 21-229 Prilosec OTC

### Carton Label (14, 28, and 42 count including outer cartons) and Trial Sample size

|                         |                                                                                                                                                                                                          |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Principal Display Panel | <ol style="list-style-type: none"><li>1. Delete the statement "NEW!" after the first 6 months of OTC marketing.</li><li>2. Delete the statement <u>                    </u> from the labeling.</li></ol> |
| Package                 | <ol style="list-style-type: none"><li>1. Identify the location of the lot number and expiration date.</li></ol>                                                                                          |

### Trial Sample Size

|                         |                                                                                                                                                                                                   |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Package Insert          | <ol style="list-style-type: none"><li>1. It is not necessary to attach the package insert to the Drug Facts label. The package insert can be included in the envelope with the mailing.</li></ol> |
| Principal display panel | <ol style="list-style-type: none"><li>1. Last sentence, revise to read: "Read label on back before use."</li></ol>                                                                                |

### Blister Card

|  |                                                                                                                                                                                                           |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <ol style="list-style-type: none"><li>1. Add the expiration date and lot number on the blister cards.</li><li>2. Add the net content statement in accordance with section 502(b)(2) of the Act.</li></ol> |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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§ 552(b)(5) Draft Labeling

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/s/

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Daniel Keravich.  
5/21/03 12:16:21 PM  
CSO

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ON ORIGINAL

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

DATE: May 2, 2003

TO: Robert Justice, M.D., Director  
Division of Gastrointestinal and Coagulation Drug Products  
HFD-180

FROM: Karen Lechter, J.D., Ph.D.  
Social Science Analyst  
Division of Surveillance, Research,  
and Communication Support, HFD-410  
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., M.P.H., Deputy Director  
Office of Drug Safety

SUBJECT: DSRCS Labeling Comprehension Study Review for Prilosec  
NDA 21-229

The following is a review by DSRCS on the Label Comprehension Study for OTC omeprazole magnesium tablets.

{See appended electronic signature page}

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## DSRCS REVIEW

**NDA#:** 21-229  
**Drug:** Omeprazole Magnesium Tablets  
**Sponsor:** Procter and Gamble Corp.  
**Document:** A Multi-Center Label Comprehension Study to Evaluate Consumer Comprehension of OTC Labeling Options for Omeprazole Magnesium Tablets  
**Reviewer:** Karen Lechter, J.D., Ph.D.  
**Reviewing Div:** HFD-410  
**Review Completed:** May 2, 2003

This is a review of a label comprehension study testing three different labels for OTC Prilosec. Participants were divided into Frequent and Infrequent heartburn sufferers, as well as low and high literacy groups.

### **Executive Summary**

Most scores were very high, regardless of the label. Scores may have been inflated due to methodological inadequacies, so comprehension in actual use may be lower than represented by these results.

In many cases, Label B scored numerically higher than the others, but by just a few points, and with questionable statistical significance. Thus, a conclusion that Label B is best overall is not overwhelmingly clear-cut.

Frequency of participants' heartburn had little effect on responses except among the Low Literate Infrequent sufferers. Self-selection questions for the subgroup of infrequent heartburn sufferers with low literacy were 10-18 points lower than for literate individuals with infrequent heartburn.

In general, the Low Literate had more difficulty with some concepts than did the Literate, with the largest differences in understanding occurring in the time of day for dosing, how often to repeat the treatment, and the time to full effect. There was no indication that literacy level substantially affected understanding of warnings that appeared on the label.

**Good understanding.** Regardless of label type, there is a good understanding of

- almost all warnings
- do not chew or crush
- stop use and contact a doctor after 14 days of treatment if heartburn persists
- contact a doctor if symptoms return in two months
- it is acceptable to use the product again after six months
- appropriate dose

**Moderate or lower understanding.** For the following issues and/or subgroups, there is moderate or low understanding:

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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Karen Lechter  
5/2/03 01:15:44 PM  
UNKNOWN

Anne Trontell  
5/2/03 02:43:35 PM  
DRUG SAFETY OFFICE REVIEWER

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 19-810  
NDA 21-229

AstraZeneca LP  
Attention: Gary P. Horowitz, Ph.D.  
1800 Concord Pike, P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Dr. Horowitz:

We acknowledge receipt on April 9, 2003 of your April 8, 2003 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

725 Chesterbrook Boulevard  
Wayne, PA 19087-5677

to

1800 Concord Pike, P.O. Box 8355  
Wilmington, DE 19803-8355

for the following new drug applications:

NDA 19-810 Prilosec® (Omeprazole) Delayed-Release Capsules  
NDA 21-229 Prilosec OTC™ (omeprazole magnesium) Delayed-Release Tablets

We revised our records to reflect this change.

Address all communications concerning these NDAs as follows:

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 19-810  
NDA 21-229  
Page 2

If you have any questions, call me at (301) 827-7450.

Sincerely,

*(See appended electronic signature page)*

Melissa Hancock Furness  
Consumer Safety Officer  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Melissa Furness  
4/16/03 09:47:20 AM

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1   Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**Labeling Review**  
**Division of OTC Drug Products**  
**HFD-560**

|                                                              |                                                  |
|--------------------------------------------------------------|--------------------------------------------------|
| <b>NDA #:</b> 21-229                                         | <b>Sponsor:</b> Procter and Gamble Company       |
| <b>Drug Product:</b> Omeprazole Magnesium Tablets            | <b># of Stock Keeping Units in Submission:</b> 5 |
| <b>Submission Dates:</b> December 20, 2002/February 24, 2003 | <b>Review Date:</b> April 14, 2003               |
| <b>Type of Submission:</b> NDA                               | <b>Reviewer:</b> Mary S. Robinson, HFD-560       |

**Background**

In response to the agency's August 8, 2002 approvable letter, on December 20, 2002, Procter and Gamble submitted proposed labeling based on the results of their label comprehension study (Study No. 22103) to demonstrate that consumers understand certain key label concepts. Full color printed labeling of the 14, 28, and 42 count cartons, configuration of outer cartons containing 28 and 42 count, configuration of plastic overlay for 42 count package, package insert, blister card, and trial sample size are included in this submission. The February 24, 2003 submission contains minor additions to the carton and blister labels. This is a review of the proposed labeling contained in these submissions. (See attachment.)

**Stock Keeping Unit:** (describe unit) 14, 28, and 42 count cartons and outer cartons containing 28 and 42 count

**Information Included in the submission follows:**

| <b>Content of Submission</b>                                                                                                                                        | <b>Yes</b> | <b>No</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|
| A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s);                           | ✓          |           |
| A table of contents or index                                                                                                                                        | ✓          |           |
| The most recent approved labeling                                                                                                                                   | ✓          |           |
| A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product. | ✓          |           |
| Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 13293.                                                                        | ✓          |           |

Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review:           Yes

**Reviewer Comments and Recommendations**

The reviewer has the following comments:

Graphic specifications for the labeling are also included and are acceptable. Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling for 14, 28, and 42 count cartons and trial sample size labeling.

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I. Carton Label (14, 28; and 42 count including outer cartons)

| Description of Paragraph Headings            | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Principal Display Panel</b>               | <ol style="list-style-type: none"> <li>1. Delete the statement "NEW!" after the first 6 months of OTC marketing.</li> <li>2. Delete the statement _____ from the labeling.</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Location of expiration date</b>           | Identify the location of the lot number and expiration date.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Use(s)</b><br><br><b>Use(s)</b>           | <ol style="list-style-type: none"> <li>1. Revise heading _____ to "Use"</li> <li>2. Revise bullet 1 to read: "treats frequent heartburn (occurs 2 or more days a week)"</li> <li>3. Delete bullets 2 and 3.</li> <li>4. Insert bullet 2 to read: "not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect"</li> </ol>                                                                                                                                                                                                                                                                                                                 |
| <b>Warning(s)</b>                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Allergy Alert</b>                         | Insert a colon behind the word "alert"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>"Do not use"</b>                          | <ol style="list-style-type: none"> <li>1. Delete bullet from the phrase " _____ " and place on the same line as "Do not use"</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>"Ask a doctor before use if you have"</b> | <ol style="list-style-type: none"> <li>1. Delete bullet 1.</li> <li>2. Revise bullet 2 to read: "[bullet] had heartburn over 3 months. This may be a sign of a more serious condition."</li> <li>3. Bullet 4. Bold the phrase "chest pain".</li> <li>4. Insert the phrase "stomach pain" as the last bullet.</li> </ol>                                                                                                                                                                                                                                                                                                                                                      |
| <b>Stop use and ask a doctor if"</b>         | <ol style="list-style-type: none"> <li>1. Delete _____</li> <li>2. Insert the following: "[bullet] your heartburn continues or worsens"</li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Directions</b>                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                              | <ol style="list-style-type: none"> <li>1. Insert the following as sentence 2. "[bullet] this product is to be used once a day, every day for 14 days "</li> <li>2. Delete the phrase " _____ " and insert the phrase "14-Day Course of Treatment" to emphasize that the drug is to be taken for 14 days.</li> <li>3. Insert bullets and move the phrases "[bullet] do not chew or crush the tablets" and "[bullet] do not crush tablets in food" up to follow bullet 3 under new heading "14-Day Course of Treatment"</li> <li>4. Make the "A" and "C" small in the phrases "adults 18 years of age and older" and "children under 18 years of age: ask a doctor"</li> </ol> |
| <b>Other information</b>                     | <ol style="list-style-type: none"> <li>1. Make the "I" in the word "information" small.</li> <li>2. Delete the phrase _____ from the storage statement.</li> <li>3. Delete the phrase _____ and insert the phrase "keep product out of high heat and humidity"</li> <li>4. Revise bullet 5 to read: "protect product from moisture"</li> </ol>                                                                                                                                                                                                                                                                                                                               |

## II. Package Insert

1. a. Move the paragraph "How Prilosec OTC Works For Your Frequent HeartBurn", so that it is the first heading.  
b. Revise the last sentence to state "Prilosec OTC is to be used once a day, every day for 14 days."
2. Under the heading "What to Expect When Using Prilosec OTC":
  - a. Revise sentences 2-5 to read: "Prilosec OTC is a different type of medicine from antacids and other acid reducers. Prilosec OTC may take 1 to 4 days for full effect, although some consumers may get relief of some symptoms sooner. Make sure you take the entire 14 days of dosing to treat your frequent heartburn."
3. Delete the word \_\_\_\_\_ from the heading \_\_\_\_\_
4. Under the new heading "Safety Record": Revise the sentence to read: "For years doctors have prescribed Prilosec to treat acid-related conditions in millions of people safely."
5. Under the heading "Who should take Prilosec OTC?" revise the sentence as follows:
6. "This product is for adults (18 years and older) with frequent heartburn — when you have heartburn 2 or more days a week.
  - Prilosec OTC is not intended for those who have heartburn infrequently, one episode of heartburn a week or less, or for those who want immediate relief of heartburn."
7. Under the heading "HOW TO TAKE PRILOSEC OTC" revise to be consistent with "Drug facts" on the carton label as follows:

### 14 DAY Course of Treatment

- Swallow 1 tablet with a glass of water \_\_\_\_\_
- Take every day for 14 days.
- Do not take more than 1 tablet a day.
- Do not chew or crush tablets.
- Do not crush tablets in food.
- Do not use for more than 14 days unless directed by your doctor.

It is important not to chew or crush these tablets, or crush the tablets in food. This decreases how well Prilosec OTC works.

### When to take Prilosec OTC Again

You may repeat a 14-day course of therapy every 4 months.

### When to talk to your doctor

Do not take for more than 14 days or more often than every 4 months unless directed by a doctor.

8. Revise the heading \_\_\_\_\_ to read: \_\_\_\_\_  
Move the paragraph with new heading to follow "\_\_\_\_\_"
9. Under the heading \_\_\_\_\_  
Revise the warnings so that they are identical to the warnings under "Drug Facts" on the carton label. (See recommendations under I, above.)

## III. Blister Card.

1. Add the expiration date and lot number on the blister cards.
2. Add the net content statement in accordance with section 502(b)(2) of the Act.
3. The sponsor made the following changes to the top of the blister card labeling.
  - a. A black box with a white background is used around the words "Do not chew or crush tablets" and "Do not crush tablets in food" instead of a black box with a black background.

b. The words "Separate at perforation" are also added to aid the consumer in opening the blister.

These changes are acceptable.

**IV. Trial Sample Size**

1. See I and II above
2. Regarding the package insert for the trial sample size, it is not necessary to attach the package insert to the drug facts label. The package insert can be included in the envelope with the mailing.
3. Principal display panel, last sentence, revise to read: "Read label on back before use."

**Reviewer's Recommendations**

1. The above stated changes in I, II, III, and IV need to be made before this supplement can be approved. A sample copy of FDA's Drug Facts labeling is attached. This example provides content information only. The labeling must comply with the format requirements of 201.66.
2. The proposed package insert has to be revised so that it is consistent with the "Drug Facts" labeling changes recommended above. A sample copy of FDA's recommendations for the package insert (content information only) is attached.

The above comments can be conveyed to the sponsor.

**IS/**

---

Mary S. Robinson, M.S.  
Regulatory Review Chemist, HFD-560

**IS/**

---

Helen Cothran,  
Team Leader, HFD-560

cc: HFD-560: CGanley/CRosebraugh/ASegal/DShetty/DKeravich/HCothran/MRobinson  
HFD-180

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

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/s/

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Mary Robinson  
5/20/03 06:04:10 PM  
INTERDISCIPLINARY

Helen Cothran  
5/21/03 01:04:37 PM  
INTERDISCIPLINARY

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# REQUEST FOR CONSULTATION

TO (Division/Office):  
Mr. Stan Lin, Lead Math Statistician  
Office of Pharmacoepidemiology and Statistical Science  
DBIII

FROM: Office of Drug Safety  
Division of Surveillance, Research and Communication Support  
Leslie Stephens, Project Manager X7-3235

|                                                                       |         |                         |                                                    |                                      |
|-----------------------------------------------------------------------|---------|-------------------------|----------------------------------------------------|--------------------------------------|
| DATE: 28 March, 2003                                                  | IND NO. | NDA NO.<br>21-229       | TYPE OF DOCUMENT<br>Complete Response to NA letter | DATE OF DOCUMENT<br>12 December 2002 |
| NAME OF DRUG: Prilosec (omeprazole magnesium) Delayed-Release Tablets |         | PRIORITY CONSIDERATION: | CLASSIFICATION OF DRUG                             | DESIRED COMPLETION DATE: 15 April 03 |
| NAME OF FIRM: Proctor and Gamble                                      |         |                         |                                                    |                                      |

### 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<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><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

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

COMMENTS/SPECIAL INSTRUCTIONS: P&G has submitted a complete response to the 8/8/02 approvable letter. The submission includes a new labeling comprehension study and revised labeling. Please see the EDR submission (\NCDSESUB1\N21229\N\_000\2002-12-20\clinstar) and respond to the following 5 questions:

1. Is label B really better than the other labels? At first glance, there appear to be few statistically significant differences.
2. Are the sample sizes appropriate for the types of analyses they are doing?
3. Was logistic regression appropriate for this analysis?
4. On p. 35 of Vol 5, is the Kappa statistic of 0.9 adequate for interrater reliability? Should they have used a larger sample of questions to test interrater reliability? See p.19 for a description of the coding process—only 3 questions were coded by both coders.
5. On p.36, under "Review of Statistical Plan," was the procedure for looking at interactions appropriate in terms of using 0.10 for the first screen and then running pairwise comparisons at  $p < 0.05$  if the interaction was not significant?

SIGNATURE OF REQUESTER: Leslie Stephens, MSN, RN; Project Manager, DSRCs  
301-827-3235 (for Karen Lechter, JD, PhD)

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 MAIL  HAND

SIGNATURE OF RECEIVER

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JAN 16 2003

IND 54,307

Proctor & Gamble  
Attention: Linda C. Jones  
Senior Scientist, Regulatory Affairs  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, OH 45040-9462

Dear Ms. Jones:

Please refer to the meeting between representatives of your firm and FDA on December 12, 2002. The purpose of the meeting was to discuss Proctor and Gamble's proposals for marketing 28-, and 42-count commercial package sizes and distributing 2-count sample packages (starter kits) to health care providers (physicians and pharmacists) and consumers with frequent heartburn under NDA 21-229 for Prilosec OTC (omeprazole magnesium) Delayed-Release Tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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JAN 15 2003

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** December 12, 2002  
**Time:** 12:15 p.m. - 1:00 p.m.  
**Location:** Parklawn Building, Conference Room "B"  
**Subject:** IND 54,307  
Omeprazole Magnesium Delayed-Release Tablets  
**Meeting Chair:** Hugo Gallo-Torres, M.D., GI Medical Team Leader, HFD-180  
**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### **FDA Attendees:**

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert Justice, M.D., Director  
Hugo Gallo-Torres, M.D., GI Medical Team Leader  
Liang Zhou, Ph.D., Chemistry Team Leader  
Arthur Shaw, Ph.D., Chemistry Reviewer  
Maria R. Walsh, M.S., Regulatory Project Manager  
Susan Daugherty, Regulatory Project Manager

#### Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director  
Daiva Shetty, M.D., Medical Officer  
Helen Cothran, Interdisciplinary Scientist/Chemist  
Mary S. Robinson, Interdisciplinary Scientist/Chemist  
Walter Ellenberg, Regulatory Project Manager

### **Sponsor Attendees:**

#### AstraZeneca, LP

Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs

#### The Proctor and Gamble Company

Thomas C. Blinn, Vice President, Global Personal health Care  
Robert A. Greene, Vice President, product Development  
Joseph A. Arcuri, General Manager, Personal Health Care NA  
Keith C. Triebwasser, Ph.D., Senior Director, Regulatory Affairs  
Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs

**Background:** NDA 21-229, Omeprazole Magnesium Delayed-Release Tablets, was resubmitted on February 12, 2002 (in response to a not approvable letter, dated November 27, 2000) for the following proposed indication: prevention of the symptoms of frequent heartburn for 24 hours. An approvable letter was issued on August 8, 2002. A teleconference was held between FDA and representatives of AstraZeneca (sponsor) and The Proctor and Gamble Co. (sponsor's agent) on August 8, 2002 to discuss the main points of the

action letter. An end-of-review meeting was held on October 9, 2002 between FDA and representatives of the sponsor and agent to discuss the action letter in more detail. During that meeting, Proctor and Gamble's intention to market various blister package sizes was discussed briefly. FDA advised the sponsor to request another meeting to discuss this issue in more detail.

Proctor and Gamble submitted a meeting request, dated October 11, 2002, and a pre-meeting briefing package, dated November 20, 2002, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for today's meeting. The package includes Proctor and Gamble's proposals for commercial package sizes and a sampling program for health care providers and consumers with frequent heartburn.

**Meeting Objective:** To discuss Proctor and Gamble's proposals for marketing 28-, and 42-count commercial package sizes and distributing 2-count sample packages (starter kits) to health care providers (physicians and pharmacists) and consumers with frequent heartburn.

**Agenda Item 1: Commercial Package Sizes**

FDA noted that the current draft labeling for Prilosec OTC (omeprazole magnesium) Delayed-Release Tablets recommends a 14-day course for the treatment of frequent heartburn. FDA asked Proctor and Gamble to provide a rationale for marketing larger than 14-count package sizes and to explain how this approach will not lead to chronic long-term use.

Proctor and Gamble made the following points:

- The results of the label comprehension study 22103 (provided in tabular format) demonstrate that consumers understand that the course of treatment is 14 days, that another 14-day course may not be started for 4 months, and to ask a doctor if heartburn continues after 14 days.
- Two or three individual 14-count cartons packaged together in a larger multi-course carton will not lead consumers to use the product any differently than if they buy two or three individual 14-count packages at the same time. The multi-course carton might reinforce the concept that each component is a separate 14-day course of treatment.
- There is no safety concern even if consumers use all three individual cartons in succession.

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FDA noted that the proposed carton includes the phrase "\_\_\_\_\_ and asked Proctor and Gamble to explain the impact of this phrase on consumers since Prilosec will be available as a prescription product as well. Proctor and Gamble said consumers might assume that the OTC product is a lower strength than the prescription product, as is the case with other acid reducers. Therefore, this phrase was added to assist consumers in making a more educated treatment choice.

**FDA comments:** FDA said the phrase indicating the number of courses of therapy on the multi-course carton label should be more prominent (e.g. larger font).

**Agenda Item 2: Sampling Program**

**A. Health Care Providers**

FDA said Proctor and Gamble's proposal to directly mail or personally detail professional samples to physicians containing a 2-count sample card (labeled on front that they are free samples, they are starter kits, and that these samples are to be followed with a 14-day regimen and including the Drug Facts label on the back of the sample card) is acceptable.

FDA asked Proctor and Gamble to explain how the sample cards will be provided to pharmacists as there is some concern that the cards will be placed on the counter for consumer pick-up. Proctor and Gamble explained that the sample cards would be directly mailed to pharmacists along with educational information for the purpose of providing pharmacists with a counseling tool to make consumers aware of the product. Proctor and Gamble confirmed that pharmacists would be instructed not to place the samples on the counter for consumer pick-up. Proctor and Gamble said copies of the package insert would be included in the sample kit for pharmacists to provide to consumers with each sample card.

**B. Consumers**

FDA asked Proctor and Gamble to provide a rationale for \_\_\_\_\_ consumers and to explain how this will not lead to chronic intermittent use.

Proctor and Gamble explained that the purpose of the sample mailing is to provide consumers with educational information on a new product and an initial product experience. The sample mailing includes a 2-count sample card (labeled on front that they are free samples, they are starter kits, and that these samples are to be followed with a 14-day regimen and including the Drug Facts label on the back of the sample card), a letter, and the package insert. Samples will be mailed only to those consumers who have self-identified through a mailed survey that they have frequent heartburn (heartburn 2 or more days a week). Sample mailings will be directed to the specific name and address of the consumers who filled out the survey and met the target population criteria. This mailing will occur only once during the market launch of the product. Proctor and

Gamble anticipates that those consumers who receive a benefit from the 2-day sample will purchase the product.

**FDA comments:**

- The starter kit package should clearly explain that appropriate use of Prilosec OTC requires 14 consecutive days of treatment and is not intended for intermittent use. Each 2-count sample card should be dispensed with the approved package insert.
- The title "Drug Facts" on the sample card should be deleted. Follow Labeling Requirements for OTC Drugs as specified in 21 CFR 201.66.
- FDA will consider whether the package insert should be attached to the sample card.
- The survey sample to be used for the identification of consumers with frequent heartburn should be included in the NDA resubmission for review.
- The 2-count sampling program proposal should be included in the NDA resubmission for final review.
- A \_\_\_\_\_ is not recommended. If the current proposal for a targeted mailing to consumers with frequent heartburn is changed, the new proposal should be submitted to FDA for review.

Minutes Preparer: Maria R. Walsh, M.S.

Chair Concurrence: Hugo Gallo-Torres, M.D.

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Meeting Minutes  
Page 5

Drafted: M. Walsh 12/19/02  
Initialed by: H. Gallo-Torres  
R. Justice  
C. Ganley

Final: M. Walsh  
Filename: I54307.minutes.12-12-02

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-229

JAN 13 2003

The Proctor & Gamble Co.  
Attention: Linda C. Jones  
Senior Scientist, Regulatory Affairs  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, OH 45040-9462

Dear Ms. Jones:

We acknowledge receipt on December 20, 2002 of your December 20, 2002 resubmission to your new drug application for Prilosec OTC (omeprazole magnesium) Delayed-Release Tablets

We consider this a complete, class 2 response to our August 8, 2002 action letter. Therefore, the user fee goal date is June 20, 2003.

If you have any question, call Maria R. Walsh, Regulatory Project Manager, at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal and Coagulation  
Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Maria Walsh  
1/13/03 11:10:04 AM

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## Division of OTC Drug Products HFD-560

|                                            |                                           |
|--------------------------------------------|-------------------------------------------|
| IND #: 54-307                              | Sponsor: Procter and Gamble Company       |
| Drug Product: Omeprazole Magnesium Tablets | # of Stock Keeping Units in Submission: 1 |
| Submission Dates: September 13, 2002       | Review Date: September 26, 2002           |
| Type of Submission: IND                    | Reviewer: Mary S. Robinson, HFD-560       |

**Background**

Procter and Gamble submitted a background package, dated September 13, 2002, in preparation for the October 9, 2002 meeting with FDA. The package included three proposed labels for final testing in a proposed label comprehension study as referenced in the agency's August 8, 2002 Action Letter. This is a review of the proposed labels contained in the September 13, 2002 submission.

**Comments**

The following are specific comments and recommendations on the proposed labels for the label comprehension study:

**I. Labels A, B, and C**

Because the labels are similar, all comments and recommendations will refer to the three labels (Label A, Label B, and Label C), except where noted. The sponsor should revise the labels so that they are in conformity with 21 CFR 201.66 -- Format and content requirements for OTC drug product labeling. The following comments about the labels refer to the guidelines and provisions of § 201.66:

1. Under "Use" the sponsor should not use capital letters in the indication statement. Refer to § 201.66(d) for format label requirements for "Drug Facts".
2. Under "Use" the sponsor should consider moving the statements "only for those who suffer heartburn 2 or more days a week" and "not intended for those who suffer occasional heartburn" to the principal display panel and to the directions section.
3. The statements under the heading "Warnings" need to be placed under an appropriate "drug facts" warnings' subheading as defined in § 201.66(c)(5) in the required order (see 21 CFR 201.66). The following changes to the labels are recommended:

(a) **Bullet 1.** Revise the statement to read: \_\_\_\_\_

(b) **Bullet 2.** To conform to the "Drug Facts" format replace the heading "Before starting treatment, see your doctor if:" with \_\_\_\_\_

(c) Label A. Under the heading \_\_\_\_\_, statement 2, make "chest pain or shoulder pain with shortness of breath or sweating; pain spreading to arms, neck or shoulders" a separate statement.

(d) Bullet 3. To conform to the "Drug Facts" format replace the heading \_\_\_\_\_ with \_\_\_\_\_

(e) The allergy alert should follow as the first statement under the heading "Warnings".

(f) Labels B and C. "Do not use" is to be the first subheading under "Warnings". However, the sponsor needs to note that this subheading allows only statements for which the contraindications are absolute. See § 201.66(c)(5)(iii).

(g) Label A. To conform with § 201.66, the information under "Stop use and ask a doctor if" should pertain to signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product.

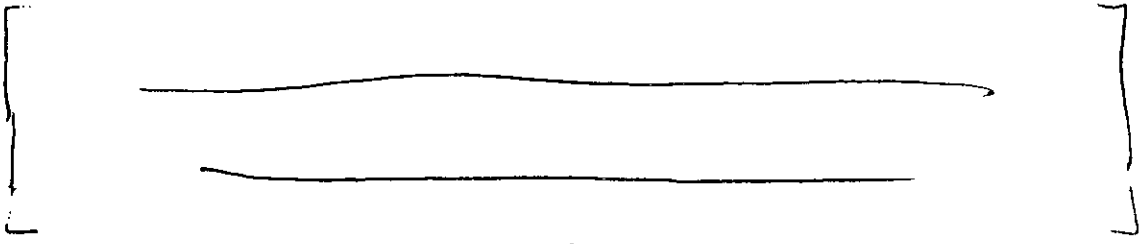
(h) Under the heading "Ask a doctor or pharmacist before use if you are" delete the hyphen in antifungal. Do not bold the word "taking". Refer to § 201.66(c) for exact format and content requirements for headings.

4. Revise the statement "Safety Feature— \_\_\_\_\_" to read: Do not use if tablet blister unit is open or torn." This statement should be placed in the labeling according to the provisions of 21 CFR 211.132—Tamper-Evident. If the tamper-evident statement is included in the "Drug Facts" section, it must be placed under "Other information."
5. Label A. Under "Directions," use shorter, simpler words/phrases where possible for the phrases: \_\_\_\_\_ and \_\_\_\_\_
6. Under "Other information," the first two bullets should be moved to "Directions" for increased visibility.
7. Under "Other information," bullet three should be revised to read: "Store at 20-25°C (68-77°F).
8. Labels B and C. Under "Directions," the statements "do not chew or crush the tablets" and "do not crush tablets in food" should be placed so that they would pertain to both courses of treatment.

## II. Package Insert

1. The proposed package insert has to be revised. The package insert at the very minimum needs to contain all of the "Drug Facts" information as written on the label. It has to list the warning conditions with their symptoms, as well as all drugs that may cause interactions with omeprazole magnesium. Information about how omeprazole magnesium is different in the onset of action, efficacy, and duration of effect compared to the other currently marketed OTC heartburn medications, should be provided for the consumer. Superiority statements should be deleted. The sponsor should state whether they are planning to test a package insert.

2. The following statements appear to be misleading:



- 3. Page 2, paragraph 1, sentence 1, delete the word "superior."
- 4. The graphics on pages 2 and 3 may not be easily understood by consumers.
- 5. Other information may also be included, for example:
  - (a) How the product works,
  - (b) What to expect during the first few days,
  - (c) Common questions with answers, if applicable,
  - (d) Expectation of benefits,
  - (e) Additional warning information, if any,

The request for the waiver, to be exempt from the requirement for the NDA safety update, should be denied.

ISI

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Mary S. Robinson, M.S.  
Regulatory Review Chemist, HFD-560

ISI

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Helen Cothran,  
Team Leader, HFD-560

cc: HFD-560: CGanley/HCothran/LShay/MRobinson  
 HFD-560: Division/File  
 Doc ID: C:\Data\Prilosec\Prilosec label comprehension 9\_13\_02\_Final  
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6 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Mary Robinson  
11/13/02 05:36:04 PM  
INTERDISCIPLINARY

Helen Cothran  
11/14/02 04:00:48 PM  
INTERDISCIPLINARY

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NDA 21-229

OCT 17 2002

The Proctor & Gamble Co.  
Attention: Linda C. Jones  
Senior Scientist, Regulatory Affairs  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, OH 45040-9462

Dear Ms. Jones:

Please refer to the meeting between representatives of your firm and FDA on June 5, 2002. The purpose of the meeting was to discuss your questions regarding the issues to be discussed at the joint meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee for the over-the-counter use of omeprazole magnesium tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** October 11, 2002  
**NDA#:** 21-229  
**IND# :** 54,307  
**NAME OF DRUG:** Prilosec OTC  
(Omeprazole Tablets) 20 mg  
**NDA HOLDER:** Proctor and Gamble Company

**I. INTRODUCTION:**

Omeprazole Delayed-release Capsules were approved under NDA 19-810 on September 14, 1989, with the proprietary name Losec. The name was changed in 1991 to Prilosec due to reports of medication errors resulting from proprietary name confusion. Proctor and Gamble submitted a new NDA for an over-the-counter (OTC) formulation of omeprazole. The sponsor submitted the proposed proprietary name of Prilosec 1 for the OTC formulation of omeprazole.

DMETS reviewed Prilosec 1 (see OPDRA consult # 00-0081) and did not recommend use of the proprietary name. This decision was based on the fact that the modifier '1' would be a source of confusion when the name was either scripted or spoken. Proctor and Gamble submitted a rebuttal and requested a reconsideration of the proposed proprietary name. In the April 3, 2002 review, DMETS noted that Proctor and Gamble's rebuttal had not provided a persuasive argument that minimized the Agency's concern with regard to potential medication errors due to confusion with the modifier '1' (see ODS consult #00-0081-1). DMETS reviewed the container label and carton labeling for possible interventions in minimizing medication errors and identified some areas of possible improvement that could minimize potential user error. These comments were also included in the April 3, 2002 DMETS review.

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), for assessment of the tradename "Prilosec OTC," regarding potential name confusion with other proprietary drug names. The previously reviewed container labels and carton labeling were re-submitted and thus will not be re-reviewed.

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## PRODUCT INFORMATION

AstraZeneca has submitted a new NDA for an over-the-counter (OTC) formulation of Omeprazole. The proposed proprietary name is Prilosec OTC. The OTC product contains the active ingredient Omeprazole Magnesium rather than Omeprazole which, is the active ingredient of the prescription product, Prilosec. The OTC product will also be formulated as a tablet rather than capsule (prescription product). Prilosec OTC will be available as a 20 mg tablet in cartons containing \_\_\_\_\_ tablets.

## II. RISK ASSESSMENT:

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Prilosec" has been utilized in the U.S. marketplace since 1991. A search was conducted of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound alike or look alike to Prilosec OTC to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database<sup>4</sup> and the Saegis<sup>5</sup> Pharma-In-Use database were also conducted. Since the proprietary name Prilosec has been used since 1991, the standard DMETS prescription analysis studies were not conducted.

The FDA Adverse Event Reporting System (AERS) was searched for any postmarketing safety reports of medication errors associated with the name Prilosec. AERS was also searched for postmarketing safety reports of medication errors associated with reports that contain the letters 'OTC' in the product name.

### A. REFERENCE SEARCH

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern.

### B. AERS DATABASE SEARCHES

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Prilosec. The MEDDRA Preferred Term (PT) "Medication Error" and the terms "Prilosec," "Omeprazole," "Prilo%," "Omep%," and "OTC%" were used as search criteria. The AERS search did not identify any reports associated with the letters "OTC" however, twenty-six actual and four potential medication error cases associated with name confusion with Prilosec were identified. The majority of

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

the actual medication error cases involved eighteen cases of name confusion between Prilosec and Prozac. Sixteen of the eighteen cases were dispensing medication errors where the prescription contained the correct label but was filled incorrectly. The two remaining cases involved one case that was filled correctly but mislabeled and the final case was mislabeled and misfilled. The remaining actual cases involved single instances of name confusion (i.e., dispensing not labeling) between Prilosec and Atacand, Prinivil, Zolofit, Accupril, Celebrex, Paxil, Warfarin, or Proscar. The four potential cases involved confusion between Prilosec and Nexium (1), or Plendil (3) but were not related to scripted look-alike or sound-alike similarities. These potential medication errors pertained to the packaging, labeling and the physical appearance of the products.

C. SAFETY EVALUATOR RISK ASSESSMENT

The 28<sup>th</sup> Edition of Dorland's Medical Dictionary defines 'OTC' in two ways. The first is over the counter, a term applied to drugs not required by law to be sold on prescription only. The second definition is: ornithine transcarbamoylase. The sponsor plans to use the 'OTC' modifier to denote an over-the-counter formulation of the prescription drug Prilosec. Although, 'OTC' can also represent an enzyme, it is not likely that this representation will cause confusion with Prilosec OTC.

A search of the AERS database identified potential name confusion between Prilosec and other products, particularly Prozac. DMETS will address the potential name confusion between Prilosec and the aforementioned products (Accupril, Atacand, Celebrex, Nexium, Paxil, Plendil, Prilosec, Prinivil, Proscar, Prozac, Warfarin, and Zolofit) in a separate post-marketing consult. Although, the AERS search identified potential cases of name confusion between Prilosec and Prozac, several factors will decrease the potential for name confusion between Prilosec OTC and Prozac. First Prozac is a prescription drug whereas Prilosec OTC will be an over-the-counter preparation, which will be available without a prescription. The majority of the medication errors involved filling or dispensing errors, which indicates that the practitioner interpreted the prescription correctly but chose the incorrect drug from the shelf. This step will be eliminated since over-the-counter medications are generally available without pharmacists' intervention. Finally, the addition of the modifier will help to distinguish Prilosec OTC from the Prozac.

Prilosec OTC appears to be the first over-the-counter product approved that contains the modifier 'OTC.' A search of the electronic NDC Directory and Orange Book did not identify any approved or marketed over-the-counter products that contain the modifier 'OTC' as a part of their proprietary name. However, neither the Division of Gastro-Intestinal and Coagulation Drug Products nor the Division of Over-the-Counter Drug Products expressed concerns with the proposed proprietary name Prilosec OTC. Additionally, DMETS' database and AERS searches did not reveal any safety concerns related to the proposed proprietary name Prilosec OTC.

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**III. RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name Prilosec OTC.
2. DMETS requests submission of the revised container labels and carton labeling for review and comment as soon as available.

This is considered a tentative decision and the firm should be notified that 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 from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/s/

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Denise Toyer, Pharm.D.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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Denise Toyer  
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PHARMACIST

Carol Holquist  
10/11/02 01:48:29 PM  
PHARMACIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

OCT 10 2002

NDA 21-229

The Proctor & Gamble Co.  
Attention: Linda C. Jones  
Senior Scientist, Regulatory Affairs  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, OH 45040-9462

Dear Ms. Jones:

Please refer to the teleconference between representatives of your firm and FDA on August 8, 2002. The purpose of the meeting was to discuss the issuance of an approvable letter.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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

DATE: October 10, 2002

TO: Maria Walsh, Project Manager  
Division of Gastrointestinal and  
Coagulation Drug Products, HFD-180

FROM: Karen Lechter, J.D., Ph.D.  
Social Science Analyst  
Division of Surveillance, Research,  
and Communication Support, HFD-410  
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., M.P.H., Director  
Division of Surveillance, Research,  
and Communication Support, HFD-410  
Office of Drug Safety

SUBJECT: DSRCS Label Comprehension Protocol Review for Omeprazole Magnesium  
Tablets for OTC Use  
IND 54,307

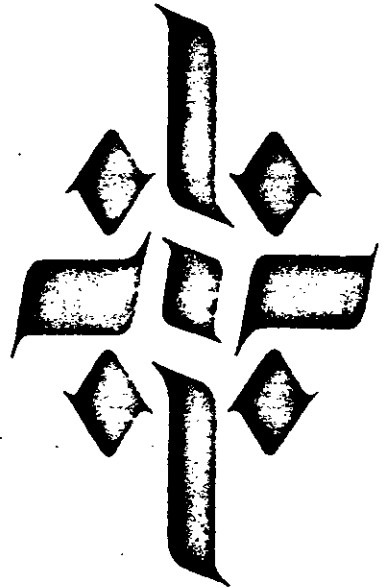
Attached is the DSRCS review of the Label Comprehension Study Protocol for  
Omeprazole Magnesium Tablets for OTC use. This review was sent to you on October  
10, 2002 in MS Word format.

Please let us know if you have any questions.

{See appended electronic signature page}

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FOOD AND DRUG ADMINISTRATION  
DIVISION OF OTC DRUG PRODUCTS  
OFFICE OF DRUG EVALUATION V  
CENTER FOR DRUG EVALUATION & RESEARCH  
5600 FISHERS LANE, HFD-560  
ROCKVILLE, MD 20857-001  
301-827-2222 (phone)  
301-827-2315(fax)



DATE 10/1/02

TO: Doug Bierer

PHONE: \_\_\_\_\_

FAX: 513 983 4380

7 PGS. (FAX + COVER)

FROM: C. Ganley

MESSAGE These are comments from the OTC Division  
for pribosec

Pribosec IND 54,307

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IND 54,307

Omeprazole magnesium, 20 mg tablets

HFD-560 and HFD-410 Comments on the Label Comprehension Study and Proposed Labels:

The following are suggestions for improvement of the proposed study protocol:

- The three proposed labels should be different enough to express the main concepts in various ways.
- The label and the package insert should carry information about the expected efficacy of the drug. It should state that \_\_\_\_\_
- The sponsor should adequately test consumer understanding of the "Use" section of the label, including expectations for the efficacy of the product.
- Questions #17, 18, and 24 should be revised, as they are leading and could bias responses.

The following are specific comments and recommendations on the proposed labels for the label comprehension study:

I. Labels A, B, and C

Because the labels are similar, all comments and recommendations will refer to the three labels (Label A, Label B, and Label C), except where noted. The sponsor should revise the labels so that they are in conformity with 21 CFR 201.66 -- Format and content requirements for OTC drug product labeling. The following comments about the labels refer to the guidelines and provisions of § 201.66:

1. Under "Use" the sponsor should not use capital letters in the indication statement. Refer to § 201.66(d) for format label requirements for "Drug Facts".
2. Under "Use" the sponsor should consider moving the statements "only for those who suffer heartburn 2 or more days a week" and "not intended for those who suffer occasional heartburn" to the principal display panel and to the directions section.
3. The statements under the heading "Warnings" need to be placed under an appropriate "drug facts" warnings' subheading as defined in § 201.66(c)(5) in the required order (see 21 CFR 201.66). The following changes to the labels are recommended:
  - a) Bullet 1 under Warnings. Revise the statement to read: ' \_\_\_\_\_

- b) Bullet 2 under Warnings. To conform to the "Drug Facts" format replace the heading \_\_\_\_\_ with "Ask a doctor before use if you have"
  - c) Label A. Under the heading \_\_\_\_\_ statement 2, make "chest pain or shoulder pain with shortness of breath or sweating; pain spreading to arms, neck or shoulders" a separate statement.
  - d) Bullet 3. To conform to the "Drug Facts" format replace the heading \_\_\_\_\_ with \_\_\_\_\_
  - e) The allergy alert should follow as the first statement under the heading "Warnings".
  - f) Labels B and C. "Do not use" is to be the first subheading under "Warnings". However, the sponsor needs to note that this subheading allows only statements for which the contraindications are absolute. See § 201.66(c)(5)(iii).
  - g) Label A. To conform with § 201.66, the information under "Stop use and ask a doctor if" should pertain to signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product.
  - h) Under the heading "Ask a doctor or pharmacist before use if you are" delete the hyphen in \_\_\_\_\_. Do not bold the word \_\_\_\_\_. Refer to § 201.66(c) for exact format and content requirements for headings.
4. Revise the statement "Safety Feature— \_\_\_\_\_" to read: "Do not use if tablet blister unit is open or torn." This statement should be placed in the labeling according to the provisions of 21 CFR 211.132—Tamper-Evident. If the tamper-evident statement is included in the "Drug Facts" section, it must be placed under "Other information."
5. Under Directions:
- (a) Label A. Under "Directions, move the fifth bullet about heartburn that continues or returns to the end of the other bullets. It breaks up the directions for use keeping it where it is.
  - (b) Labels B and C. Change the word \_\_\_\_\_ to a simpler term unless testing shows it is adequately understood.
  - (c) Use alternative wording to \_\_\_\_\_ and \_\_\_\_\_. This terminology is not common and may not be understood by some readers.
  - (d) Consider stating whether it is necessary to eat in the morning after taking the product. The study might test if people are confused on that issue due to the instruction to take before eating in the morning. Some people do not eat until lunch time.
6. Under "Other information," the first two bullets should be moved to "Directions" for increased visibility.
7. Under "Other information," bullet three should be revised to read: "Store at 20-25°C (68-77°F).

- 8. Labels B and C. Under "Directions," the statements "do not chew or crush the tablets" and "do not crush tablets in food" should be placed so that they would pertain to both courses of treatment.

II. Package Insert

The proposed package insert has to be revised. The package insert at the very minimum needs to contain all of the "Drug Facts" information as written on the label. It has to list the warning conditions with their symptoms, as well as all drugs that may cause interactions with omeprazole magnesium. Information about how omeprazole magnesium is different in the onset of action, efficacy, and duration of effect compared to the other currently marketed OTC heartburn medications, should be provided for the consumer. Superiority statements should be deleted.

Overall, the package insert should be less promotional and should be simplified to be understandable to the greatest number of readers. Simplification would include

- using shorter, simpler words where possible, for words such as \_\_\_\_\_ and others
- avoiding slang terms, such as "\_\_\_\_\_"
- explaining terms that consumers may not know, such as "acid pump," "placebo" "course of therapy," and "OTC"
- using text, rather than bar charts to explain effectiveness, unless testing shows the charts are understandable
- removing pictographs, such as the one for telephoning the doctor, which have not tested and shown to be universally understood.

One piece of advice in the label is to notify the doctor if '\_\_\_\_\_'. This bullet is confusing. Either consumers believe they have heartburn, or they do not. If they have symptoms of heartburn, this bullet appears to advise them to tell a doctor. Consumers are not in a position to know that their symptoms are not really heartburn, but may be something else. Either this bullet should be eliminated, or its message should be clarified.

Under '\_\_\_\_\_' it does not clearly say to stop use; it merely says to talk to the doctor. If it is about when to stop, the text should indicate that the consumer should stop use as well as talk to the doctor.

The following statements appear to be misleading and may need further qualification:

- (a) \_\_\_\_\_
- (b) \_\_\_\_\_
- (c) \_\_\_\_\_
- (d) \_\_\_\_\_
- (e) \_\_\_\_\_

Page 2, paragraph 1, sentence 1, delete the word ~~\_\_\_\_\_~~

The graphics on pages 2 and 3 may not be easily understood by consumers.

Other information may also be included, for example:

- (a) How the product works,
- (b) What to expect during the first few days,
- (c) Common questions with answers, if applicable,
- (d) Expectation of benefits,
- (e) Additional warning information, if any.

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DSRCS Comments on the Proposed Label Comprehension Study

IND# 54,307

Omeprazole Magnesium Tablets

**Comments on the Methodology**

We suggest excluding persons who are currently using or have used Prilosec in the past.

**Comments on Statistical Analysis and Coding**

The sponsor plans to use logistic regression using  $p \leq 0.10$ . The OTC Division will consult a statistician and will comment on whether logistic regression and the other planned tests are appropriate, if the sample sizes are adequate, and whether  $p$  should be  $\leq 0.05$ .

The sponsor plans to use a single coding coordinator to code all open-ended questions. According to the sponsor, this will reduce variability and coder bias. If more than one coder is needed, the two will work side-by-side. While this technique may help increase consistency, it may reduce external validity if there is only one coder. Further, it will not reduce bias if the coder is biased. If all questions or a sample of questions are coded the same way by two persons, there is more basis to conclude that the categories have external validity. I recommend more than one coder on at least a sample of the questions.

Responses will be coded as correct (correct initially or after probes), acceptable (not what label directs, but not incorrect in terms of product usage), or incorrect.

**Comments on the Questionnaire**

The following bullets describe suggestions for the questionnaire. If additional changes are made to the label, those changes should be tested, if appropriate.

- Questions about education and income are not necessary. The literacy test will be sufficient to classify persons according to ability to read the labels.
- Q.10 is a multiple choice question asking about the indication. We suggest adding an additional choice that would encompass both treatment of frequent heartburn (b) and \_\_\_\_\_, (d). This could be done by adding a choice "both b and d" or something like "Treatment \_\_\_\_\_ of any heartburn." Alternatively, participants could be instructed to check all that were correct in the list. We propose this change to learn if consumers believe the product is for more purposes than indicated on the label. As currently worded, the question suggests that only one of the uses is correct. Some consumers may not understand that from the label.
- The self-selection question (Q.11) asks "\_\_\_\_\_ We believe \_\_\_\_\_ suggests it is imperative that they use it, which is not the case. We suggest rewording that question to ask if they "could" use it, or, using wording similar to that used in later questions, ask if it "is OK or not OK" for the person to use this product for their heartburn.
- Q.13 is somewhat leading. It is asked if Q.11 is answered incorrectly. It tells participants to think about how often they experience heartburn and think about the

label, and then it asks again if they should use the product. The results of this question, because it is leading, may not be greatly informative other than to determine if participants can understand the number of times a week they should experience heartburn before using this product. The responses will not tell us if there are other reasons on the label that would cause participants to say they should not use the product. Also, like Q.11, the wording should be changed to "could" or "OK or not OK." Participants should be asked why they gave the response they did to determine which aspects of the label drove their decision.

- We suggest that the scenario questions be about a third person, not the participants imagining situations happening to themselves. We suggest this because it is possible participants will take into consideration aspects of their own situation that are not relevant to the question. Therefore, we suggest phrasing the scenarios in terms of Jim or Jane or some other person and ask the questions in terms of how those persons should behave under the circumstances given.
- Q.15 and Q.16 should use the same wording as Q.14.
- Wording in the scenarios should be simplified as much as possible, as they will be read by persons who may have difficulty reading. Therefore, in Q.15, change \_\_\_\_\_ to "right away" and rephrase the question appropriately. In Q.30, Cards L and M, change \_\_\_\_\_ to "days in a row." In Card M, change \_\_\_\_\_ to "passed."
- Include more questions in which a person wants to use the product for episodic relief or episodic prevention. Currently, there is only one such question for relief and one for prevention. As this may be a concept that is misunderstood, we suggest asking about it in more questions as an internal validity check.
- Include a scenario in which a person takes the product for fewer than 14 days to determine what consumers believe is appropriate in terms of length of treatment. What do they believe should be done if symptoms go away after a few days?
- For Q.18, use only one of the symptoms listed (lightheaded, dizzy, or sweating). The label suggests that any one of those should trigger a talk with the doctor. It would be better not to include all of them, thus mirroring the language on the label, to see if consumers realize any one of them is a trigger to involve the doctor. If the label changes in this respect, the question should test the revised wording.
- There should be more scenarios interspersed that the sponsor refers to as "dummy questions." These are used to avoid a series of questions that all require the same response. One such question could appear before Q20 and ask about a situation in which it is OK to continue taking the product. Other dummy questions should be added, as well.
- In some scenarios, there is reference to "frequent heartburn 2 or more days a week." This phrase is redundant. We suggest taking out the word "frequent" because of the redundancy and because it gives participants a diagnosis. They would not have such a diagnosis if they were considering purchasing the product in a store. However, they would know how often they suffer heartburn symptoms.
- We suggest adding a question before Q20 in which heartburn has gone away. Then Q20, in which heartburn has not gone away can be asked.
- Q21 should limit symptoms to chest pain with one other symptom (other than shortness of breath), to determine if participants understand the correct combination

of symptoms needed to trigger a consultation with a physician. This item on the label does not appear to communicate clearly. Another question should address chest pain with shortness of breath and no other symptom. This question should be revised if, as recommended, this part of the label is reworded. The question (or questions) should present scenarios that may reflect ways in which the label could be misinterpreted on this issue.

- Q.28, asking how often a 14-day course of therapy can be repeated, should not be asked at all or should be asked after the scenario dealing with that issue. Otherwise this question can influence responses to the scenario question, which is of more interest.
- Q.29 about chewing or crushing the product should be put in the form of scenarios rather than yes/no questions. Alternatively, but less useful than a scenario, would be to have a question listing a number of things you can do with the tablet and ask participants to check those that apply. The list should include some things that could be done and some that should not be done. However, it would be better to ask these issues in scenarios to see if they can apply the information appropriately.
- There should be a question about use with one or more of the medications listed on the label that require physician consultation.
- Additional concepts should be considered for inclusion, including the following:
  - **Frequent heartburn can be a sign of a serious condition.** There are several ways to ask such a question. One is by multiple choice, asking participants to check all that apply in the following question:  
 "Heartburn 2 or more times a week
    - can be ...
    - can be...
    - can be..
    - can be a sign of a more serious condition
    - can be..."

Some of the choices would be true according to the label, and some false. Alternatively, other ways of asking about this concept could be used.

- **The product may not begin to work for days.** This concept should be included if discussions between FDA and the sponsor conclude it should be on the label. Do consumers understand the effects of Prilosec may not be evident right away? Do they understand it is not effective for immediate relief? Do they believe they can use other products for immediate relief while waiting for Prilosec to be effective?

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... If the label is revised as discussed in the meeting of October 9, 2002, this may not need to be tested.

- **Alternative wording for new messages.** Some of the changes that will be made to the label should be tested for the best way to express the information.
- Different ways of presenting the warning information should be considered.

## DSRCS REVIEW

**IND#:** 54,307  
**Drug:** Omeprazole Magnesium Tablets  
**Sponsor:** Proctor and Gamble Co.  
**Study:** Label Comprehension Study Protocol  
**Study Report Date:** September 5, 13, and 17, 2002  
**Reviewer:** Karen Lechter, J.D., Ph.D.  
**Reviewing Div:** HFD-410  
**Review Completed:** October 9, 2002

### **Summary**

This review presents comments from the Division of Surveillance, Research, and Communication Support, Office of Drug Safety, on the proposed questionnaire, the test labels, and the package insert.

### **Background**

After the Advisory Committee meeting and the FDA Action Letter and conference call of August 8, 2002, the sponsor conducted an iterative series of testing with 30 different labels using 200 individual interviews with heartburn sufferers. The sponsor also conducted two different label comprehension tests with 647 and 741 participants, respectively. The second study took place after August 8. The sponsor used the results of these tests to develop the three versions of the label to be tested in this label comprehension study. The sponsor did not send the results of these developmental tests to the agency. The sponsor has changed the label and has developed this study to address the Agency's concerns expressed in the Action Letter of August 8, 2002 and conference call on that date.

Three primary concepts were explored in the most recent interviews and testing:

1. The product is intended for those who experience frequent heartburn, not for the immediate treatment of heartburn or prevention of heartburn due to food or beverage.
2. The product should not be used for more than \_\_\_\_\_ courses of treatment in one year at \_\_\_\_\_ month intervals, or used for more than 14 days, unless directed by a doctor.
3. Individuals with co-existing warning signs understand the actions they may need to take relative to the use of the product and/or contacting a doctor.

### **Communication Objectives**

The sponsor made label changes as a result of the testing. Based on the earlier research, the sponsor is using a variety of approaches to emphasize certain ideas on the label, including bolding, capitalization, underlining, and highlighting. For some issues, the sponsor varied the different versions of the labels in terms of emphasis, wording, and grouping of information, to test which version communicates best. The following are the key communication objectives:

- Uses
  - For adults with frequent heartburn

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- Not for relief or prevention of episodic heartburn
- Warnings
  - Understand when to see the doctor before and after starting treatment.
  - Ask a doctor before use if have label warning symptoms
- Directions
  - Understand directions
  - Understand when can take additional courses of treatment without physician intervention

**Comments on the Methodology**

The Medical Officer in the OTC Division has presented the methodology in her report. We suggest excluding persons who are currently using or have used Prilosec in the past.

**Comments on Statistical Analysis and Coding**

The sponsor plans to use logistic regression using  $p \leq 0.10$ . The OTC Division will consult a statistician and will comment on whether logistic regression and the other planned tests are appropriate, if the sample sizes are adequate, and whether  $p$  should be  $\leq 0.05$ .

The sponsor plans to use a single coding coordinator to code all open-ended questions. According to the sponsor, this will reduce variability and coder bias. If more than one coder is needed, the two will work side-by-side. While this technique may help increase consistency, it may reduce external validity if there is only one coder. Further, it will not reduce bias if the coder is biased. If all questions or a sample of questions are coded the same way by two persons, there is more basis to conclude that the categories have external validity. I recommend more than one coder on at least a sample of the questions.

Responses will be coded as correct (correct initially or after probes), acceptable (not what label directs, but not incorrect in terms of product usage), or incorrect.

**Comments on the Questionnaire**

The following bullets describe suggestions for the questionnaire. If additional changes are made to the label, those changes should be tested, if appropriate.

- Questions about education and income are not necessary. The literacy test will be sufficient to classify persons according to ability to read the labels.
- Q.10 is a multiple choice question asking about the indication. We suggest adding an additional choice that would encompass both treatment of frequent heartburn (b) and \_\_\_\_\_ (d). This could be done by adding a choice "both b and d" or something like "Treatment \_\_\_\_\_ of any heartburn." Alternatively, participants could be instructed to check all that were correct in the list. We propose this change to learn if consumers believe the product is for more purposes than indicated on the label. As currently worded, the question suggests that only one of the uses is correct. Some consumers may not understand that from the label.
- The self-selection question (Q.11) asks \_\_\_\_\_ "We believe \_\_\_\_\_ suggests it is imperative that they use it,

which is not the case. We suggest rewording that question to ask if they "could" use it, or, using wording similar to that used in later questions, ask if it "is OK or not OK" for the person to use this product for their heartburn.

- Q.13 is somewhat leading. It is asked if Q.11 is answered incorrectly. It tells participants to think about how often they experience heartburn and think about the label, and then it asks again if they should use the product. The results of this question, because it is leading, may not be greatly informative other than to determine if participants can understand the number of times a week they should experience heartburn before using this product. The responses will not tell us if there are other reasons on the label that would cause participants to say they should not use the product. Also, like Q.11, the wording \_\_\_\_\_ be changed to "could" or "OK or not OK." Participants : \_\_\_\_\_ be asked why they gave the response they did to determine which aspects of the label drove their decision.
- We suggest that the scenario questions be about a third person, not the participants imagining situations happening to themselves. We suggest this because it is possible participants will take into consideration aspects of their own situation that are not relevant to the question. Therefore, we suggest phrasing the scenarios in terms of Jim or Jane or some other person and ask the questions in terms of how those persons should behave under the circumstances given.
- Q.15 and Q.16 should use the same wording as Q.14.
- Wording in the scenarios should be simplified as much as possible, as they will be read by persons who may have difficulty reading. Therefore, in Q.15, change \_\_\_\_\_ to "right away" and rephrase the question appropriately. In Q.30, Cards L and M, change ' \_\_\_\_\_ to "days in a row." In Card M, change \_\_\_\_\_ to "passed."
- Include more questions in which a person wants to use the product for episodic relief or episodic prevention. Currently, there is only one such question for relief and one for prevention. As this may be a concept that is misunderstood, we suggest asking about it in more questions as an internal validity check.
- Include a scenario in which a person takes the product for fewer than 14 days to determine what consumers believe is appropriate in terms of length of treatment. What do they believe should be done if symptoms go away after a few days?
- For Q.18, use only one of the symptoms listed (lightheaded, dizzy, or sweating). The label suggests that any one of those should trigger a talk with the doctor. It would be better not to include all of them, thus mirroring the language on the label, to see if consumers realize any one of them is a trigger to involve the doctor. If the label changes in this respect, the question should test the revised wording.
- There should be more scenarios interspersed that the sponsor refers to as "dummy questions." These are used to avoid a series of questions that all require the same response. One such question could appear before Q20 and ask about a situation in which it is OK to continue taking the product. Other dummy questions should be added, as well.
- In some scenarios, there is reference to "frequent heartburn 2 or more days a week." This phrase is redundant. We suggest taking out the word "frequent" because of the redundancy and because it gives participants a diagnosis. They would not have such

a diagnosis if they were considering purchasing the product in a store. However, they would know how often they suffer heartburn symptoms.

- We suggest adding a question before Q20 in which heartburn **has** gone away. Then Q20, in which heartburn **has not** gone away can be asked.
- Q21 should limit symptoms to chest pain with one other symptom (other than shortness of breath), to determine if participants understand the correct combination of symptoms needed to trigger a consultation with a physician. This item on the label does not appear to communicate clearly. Another question should address chest pain with shortness of breath and no other symptom. This question should be revised if, as recommended, this part of the label is reworded. The question (or questions) should present scenarios that may reflect ways in which the label could be misinterpreted on this issue.
- Q.28, asking how often a 14-day course of therapy can be repeated, should not be asked at all or should be asked after the scenario dealing with that issue. Otherwise this question can influence responses to the scenario question, which is of more interest.
- Q.29 about **chewing or crushing** the product should be put in the form of scenarios rather than yes/no questions. Alternatively, but less useful than a scenario, would be to have a question listing a number of things you can do with the tablet and ask participants to check those that apply. The list should include some things that could be done and some that should not be done. However, it would be better to ask these issues in scenarios to see if they can apply the information appropriately.
- There should be a question about use with one or more of the medications listed on the label that require physician consultation.
- Additional concepts should be considered for inclusion, including the following:
  - **Frequent heartburn can be a sign of a serious condition.** There are several ways to ask such a question. One is by multiple choice, asking participants to check all that apply in the following question:  
"Heartburn 2 or more times a week
    - can be ...
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Some of the choices would be true according to the label, and some false. Alternatively, other ways of asking about this concept could be used.

- **The product may not begin to work for      days.** This concept should be included if discussions between FDA and the sponsor conclude it should be on the label. Do consumers understand the effects of Prilosec may not be evident right away? Do they understand it is not effective for immediate relief? Do they believe they can use other products for immediate relief while waiting for Prilosec to be effective?
- **How to take the product if you don't eat breakfast.** Are participants confused about the instruction to take it before eating in the morning? Do they interpret the label as suggesting they must have something to eat? What should people

who don't eat breakfast do? If the label is revised as discussed in the meeting of October 9, 2002, this may not need to be tested.

- **Alternative wording for new messages.** Some of the changes that will be made to the label should be tested for the best way to express the information.
- Different ways of presenting the warning information should be considered. The OTC division may be able to provide advice on this issue.

#### Suggestions for the label

##### **Uses**

- Consider not using all capital letters for the words "TREATMENT" and "FREQUENT HEARTBURN." Studies suggest all capitals are difficult to read. Was this feature of the label tested in the iterative testing? If not, DSRCS suggests testing at least one version of the label using a different type of emphasis for these words, other than all capitals.
- Include a statement to the effect that it is not for immediate relief, that it takes one to two days to notice the effects, on at least one version of the labels to be tested.

##### **Directions**

- Move the bullet about heartburn that continues or returns to the end of the other bullets. It breaks up the directions for use keeping it where it is. For Labels B and C, put the bullets about *not chewing or crushing the tablets* at the end of the section on the first course of treatment.
- Change the word "frequently" to "often" unless testing shows it is adequately understood.
- Use alternative wording to "\_\_\_\_\_ and \_\_\_\_\_" This terminology is not common and may not be understood by some readers.
- Consider stating whether it is necessary to eat in the morning after taking the product. The study might test if people are confused on that issue due to the instruction to take before eating in the morning. Some people do not eat until lunch time.

##### **Ask a doctor before use if you have**

- Make it clear that "chest pain or shoulder pain" must accompany the symptoms listed after those words. As it is now written, it appears that one item is "chest pain or shoulder pain with shortness of breath," and each subsequent item can stand on its own and need not accompany chest or shoulder pain.
- The bullet should reflect that lightheadedness, sweating and dizziness should occur together to trigger checking with a doctor.
- The OTC division may have further comments about this section.

#### Suggestions for the Package Insert

Overall, the package insert should be less promotional and should be simplified to be understandable to the greatest number of readers. Simplification would include

- using shorter, simpler words where possible, for words such as "medication," "experiencing," and others
- avoiding slang terms, such as \_\_\_\_\_

- explaining terms that consumers may not know, such as "acid pump," "placebo" "course of therapy," and "OTC"
- using text, rather than bar charts to explain effectiveness, unless testing shows the charts are understandable
- removing pictographs, such as the one for telephoning the doctor, which have not tested and shown to be universally understood.

One piece of advice in the label is to notify the doctor if \_\_\_\_\_

\_\_\_\_\_ This bullet is confusing. Either consumers believe they have heartburn, or they do not. If they have symptoms of heartburn, this bullet appears to advise them to tell a doctor. Consumers are not in a position to know that their symptoms are not really heartburn, but may be something else. Either this bullet should be eliminated, or its message should be clarified.

Under "When to stop use" it does not clearly say to stop use; it merely says to talk to the doctor. If it is about when to stop, the text should indicate that the consumer should stop use as well as talk to the doctor.

#### **Summary**

This review suggests changes for the questionnaire, the methodology, the label, and the package insert.

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** October 9, 2002  
**Time:** 11:30 a.m. - 1:00 p.m.  
**Location:** Parklawn Building, Chesapeake Conference Room

**Application:** IND 54,307  
Omeprazole Magnesium Tablets

**Sponsor:** AstraZeneca, LP/Proctor and Gamble Company

**Type of Meeting:** End-of-Review Meeting

**Meeting Chair:** Charles Ganley, M.D. Division Director, HFD-560

**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### FDA Attendees:

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., Director

Office of Drug Evaluation V (HFD-105)

Jonca Bull, M.D., Director

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert Justice, M.D., Director  
Hugo Gallo-Torres, M.D., GI Medical Team Leader  
Maria R. Walsh, Regulatory Project Manager  
Liang Zhou, Ph.D., Chemistry Team Leader  
Arthur Shaw, Ph.D., Chemistry Reviewer

Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director  
Daiva Shetty, M.D., Medical Officer  
David Hilfiker, Chief, Project Management Staff  
Helen Cothran, Interdisciplinary Scientist/Chemist  
Mary S. Robinson, Interdisciplinary Scientist/Chemist

Division of Pharmacological Evaluation II (HFD-870)

Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Surveillance, Research, and Communication Support (HFD-410)

Karen Lechter, J.D., Ph.D., Social Science Analyst

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**Sponsor Attendees:**

AstraZeneca LP

Douglas Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs

The Proctor and Gamble Company

Thomas C. Blinn, Vice President, Global Personal Health Care  
Robert A. Greene, Vice President, Product Development  
Joseph A. Arcuri, General Manager, Personal Health Care NA  
Keith C. Triebwasser, Ph.D., Senior Director, Regulatory Affairs  
Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs

**Background:** NDA 21-229, Omeprazole Magnesium Tablets, was resubmitted on February 12, 2002 (in response to a not approvable letter, dated November 27, 2000) for the following proposed indication: prevention of the symptoms of frequent heartburn for 24 hours. This application was discussed at the joint meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee on June 21, 2002. An approvable letter was issued on August 8, 2002. A teleconference was held between FDA and representatives of the sponsor on August 8, 2002 to discuss the main points of the action letter. FDA recommended the sponsor request an end-of review meeting to discuss the action letter in more detail.

The Proctor and Gamble Company (agent for the sponsor, AstraZeneca) submitted a meeting request, dated August 28, 2002, and a pre-meeting briefing package, dated September 13, 2002, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for today's meeting. The package included annotation of the August 8, 2002 action letter and a list of five discussion topics.

**Meeting Objective:** To discuss the following topics: 1) The concept that omeprazole magnesium tablets may take        days to work; 2) Diazepam and digoxin drug-drug interactions; 3) The proposed label comprehension study, the proposed labels, and the revised package insert; 4) The proposed tradename; and 5) NDA resubmission review and final approval timing.

**Agenda Item 1:**        "May take        days to work"

Proctor and Gamble's position is that this concept is not necessary or appropriate to convey in the label for the following reasons:

- Based on the label comprehension study (02255) and the actual use study (2001007), Proctor and Gamble states the vast majority of consumers understand that the product is to be taken on a regimen basis and comply with the 14-day regimen.

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- Proctor and Gamble states the results of the pivotal clinical trials demonstrate that the drug provides a statistically and clinically significant effect (prevention of heartburn in the 24 hours) following the first dose of a 14-day regimen.

Discussion:

FDA made the following points:

- The Joint Advisory Committee recommended incorporation of this concept into the label.
- Although a treatment effect may be demonstrated on the first day, maximum effect may not be reached until a few days later. Therefore, consumers need to understand that they may not experience a clinical benefit on the first day.
- Consumers need to understand that this drug product is not intended for: 1) immediate relief of heartburn; 2) the treatment of occasional heartburn; or 3) the prevention of heartburn brought on by eating certain foods or beverages.
- Consumers need to understand that they must take this drug product for 14 days for treatment of the condition, "frequent heartburn."

A discussion ensued about the wording of this concept and its location on the label. To address FDA's concerns and demonstrate correct self-selection, Proctor and Gamble proposed testing the following three bullets in the *Uses* section of the label:

- Not intended for those who suffer occasional heartburn
- Not intended for those who suffer heartburn fewer than 2 days per week
- Not intended for:
  - immediate treatment of heartburn
  - prevention of heartburn brought on by eating or drinking certain food or beverages

In addition, Proctor and Gamble proposed testing a reference statement to the package insert about how the drug product works.

FDA said the concept that the drug product may take \_\_\_\_\_ days to work should be explicitly tested in the label rather than just a reference statement to the package insert about how the drug product works. This concept could be located in the *Directions* section rather than the *Uses* section, if preferred.

**Agenda Item 2: Diazepam and digoxin drug-drug interaction**

Proctor and Gamble's position is that diazepam and digoxin do not pose any clinically significant interaction with omeprazole magnesium and therefore these interactions do not need to be included in the labeling.

Discussion:

FDA said omeprazole increases the AUC of diazepam by 70% and therefore this drug-drug interaction must be included in the labeling.

In support of its position, Proctor and Gamble cited a drug-drug interaction study with cimetidine and diazepam in which the AUC of diazepam was increased by 60-70%. However, cognitive testing showed no statistically significant difference between those subjects taking cimetidine and diazepam as compared to those subjects taking diazepam alone. FDA said this study (Greeblatt et al, 1984) included only 10 subjects all less than 50 years of age who were taking diazepam for several months. Elderly consumers are more likely to experience clinical consequences of increases in AUC by 70%. The Division of Neuropharmacological Drug Products concurred that this drug-drug interaction may have clinical significance and recommended its inclusion in the labeling for omeprazole magnesium.

As a result of this discussion, Proctor and Gamble agreed to include the diazepam drug interaction in the labeling for now.

FDA said its final recommendation regarding the drug-drug interaction with digoxin would be provided at a later time pending comments from the Division of Cardio-Renal Drug Products.

**Agenda Item 3:** Proposed label comprehension study, proposed labels, and revised package insert

Proctor and Gamble submitted the following to IND 54,307: 1) a draft label comprehension study, dated September 5, 2002; 2) proposed labels, dated September 13, 2002; 3) proposed questions/scenarios for the label comprehension study, dated September 17, 2002; and 4) a revised package insert, dated September 19, 2002.

FDA plans to provide a comprehensive list of comments regarding the proposed label comprehension study, proposed labels, and revised package insert to Proctor and Gamble later today by facsimile.

The following comments were conveyed at the meeting:

Proposed Label:

- label must conform to the format specified in 21 CFR 201.66

Proposed Label Comprehension Study:

- more than one coding coordinator on all open-ended questions is recommended
- scenario questions should be phrased in term of a third person

- additional "dummy questions" should be interspersed in the scenarios
- questions about chewing or crushing the product should be used in the form of scenarios
- a question about use with one or more of the medications listed on the label that requires physician consultation should be included
- questions about the following concepts should be included: 1) frequent heartburn could be a sign of a serious condition; 2) the product may not begin to work for — days; 3) use with other acid reducers; and 4) how to take the product if you don't eat breakfast

Discussion: Proctor and Gamble pointed out that consumer understanding increases if brandnames are used on the label. FDA said using brandnames on the label presents a legal problem regarding trademark and is therefore not recommended.

There was some discussion about food effect and when it is best to take the product. It was decided that the label should specify that it is best to take the product before eating.

Revised Package Insert:

- contents should be less promotional
- language should be simplified
- contents should include all information that is on the label

Discussion: FDA confirmed that the package insert does not need to be tested in a comprehension study.

**Agenda Item 4: Revised product tradename**

Proctor and Gamble submitted two new proposed tradenames to IND 54,307, dated August 28, 2002, for FDA review. Proctor and Gamble's first choice of proposed tradenames is "Prilosec OTC" and the second choice is \_\_\_\_\_

Discussion:

FDA said the proposed tradename, "Prilosec OTC," is acceptable. FDA recommended that Proctor and Gamble submit the proposed carton labeling showing the graphics, color, logo, and exact size of the lettering. FDA confirmed that this information may be submitted to IND 54,307.

**Agenda Item 5: NDA resubmission review and final approval timing**

Proctor and Gamble plans to resubmit the NDA between mid-December 2002 and early January 2003 and inquired whether the resubmission would be considered a Class 1 or Class 2 resubmission.

Discussion:

FDA said the resubmission would be considered a Class 2 resubmission with a six-month review time. FDA explained that a Class 1 resubmission includes items such as final printed labeling, draft labeling, safety updates, assay validation data, final release testing, and other minor clarifying data. Since the resubmission for this drug product will include the results of a new label comprehension study, it would be considered a Class 2 resubmission. FDA referred Proctor and Gamble to the Guidance for Industry, "Classifying Resubmissions in Response to Action Letters."

**Miscellaneous:**

1. Blister Package Sizes: Proctor and Gamble's \_\_\_\_\_

\_\_\_\_\_ was discussed briefly. FDA said only the 14-count package will be considered for approval in the next review cycle because that is the package size studied in the actual use study. FDA explained that consumer compliance with a 14-day treatment regimen might be problematic with the availability of different package sizes (e.g., consumers may take the product less than 14 days or may use the product intermittently for many courses per year). Therefore, data from an actual use study must be provided for each package size to ensure correct consumer usage.

Proctor and Gamble said larger package sizes (e.g. 28- and 42-count) would allow for multiple cycles of use as allowed on the label, similar to Tylenol, for example. FDA said use of omeprazole magnesium tablets differs from that of Tylenol. Tylenol is indicated for intermittent use and the label directs the consumer to talk to a doctor if more than 10 days of use is needed. Omeprazole magnesium is not indicated for intermittent use but rather is indicated for a 14-day cycle of treatment, similar to vaginal antifungal drug products. In this case, use of a different package size must be studied in an actual use study.

FDA advised Proctor and Gamble to request another meeting to discuss this issue in more detail.

2. Waiver Request for Safety Update Report: Proctor and Gamble submitted a waiver request regarding the submission of a safety update report to IND 54,307, dated September 19, 2002. FDA said the NDA resubmission should include a safety update and therefore, the request for a waiver is denied. If there are no ongoing or recently completed studies utilizing the proposed drug product or if there are no changes to the safety profile from worldwide prescription experience with the proposed drug product since the last safety update, then the new safety update can reflect this information.
3. Communication: FDA reminded Proctor and Gamble that all communication with FDA should be directed to the Division of Gastrointestinal and Coagulation Drug Products,

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through the Project Manager, Maria Walsh.

Minutes Preparer: Maria R. Walsh, M.S.

Chair Concurrence: Charles Ganley, M.D.

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**Meeting Minutes**

**Page 8**

**Drafted: M. Walsh 10/31/02**

**Initialed by: D. Shetty 11/19/02**

**C. Ganley 11/19/02**

**J. Bull 11/19/02**

**F. Houn 11/1/02**

**K. Lechter 11/4/02**

**S. Al-Fayoumi 11/7/02**

**L. Zhou 11/7/02**

**H. Gallo-Torres 11/7/02**

**R. Justice 11/8/02**

**Final: M. Walsh 11/19/02**

**Filename: I54307.minutes.10-9-02**

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Charles Ganley  
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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

**DATE RECEIVED:** September 3, 2002

**DUE DATE:** October 11, 2002

**ODS CONSULT #:** 00-0081-2

**TO:** Robert Justice, M.D.  
Director, Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)

**THROUGH:** Maria Walsh  
Project Manager  
HFD-180

**PRODUCT NAME:**  
Prilosec OTC  
(Omeprazole Tablets)  
20 mg

**NDA SPONSOR:**  
Proctor and Gamble Company

**NDA#:** 21-229  
**IND# :** 54,307

**SAFETY EVALUATOR:** Denise P. Toyer, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Prilosec OTC" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** DMETS has no objections to the use of the proprietary name, Prilosec OTC.

DMETS requests submission of the revised container labels and carton labeling for review and comment as soon as available.

This name, along 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 from the signature date of this document.

/s/

/s/

Carol Holquist, RPh  
Deputy Director,  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

## MEMORANDUM OF TELECON

DATE: August 8, 2002

APPLICATION NUMBER: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets

BETWEEN:

Office of Drug Evaluation III (HFD-103)

Florence Houn, M.D., Director

Office of Drug Evaluation V (HFD-105)

Jonca Bull, M.D., Director

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., Acting Director

Maria R. Walsh, M.S., Regulatory Project Manager

Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director

Linda Katz, M.D., Deputy Director

Walter Ellenberg, Regulatory Project Manager

AND

Proctor and Gamble

Thomas Blinn, VP Global Personal Health Care

Robert Greene, VP Personal Health Care R&D

Nora Zorich, M.D., Ph.D., Medical Director, Health Care

Keith Triebwasser, Ph.D., Senior Director, Regulatory Affairs

Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs

Linda Jones, Senior Scientist, Regulatory Affairs

AstraZeneca LP

Doug Levine, M.D., Chief Medical officer, Gastrointestinal Therapeutic Area

Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs

SUBJECT: Issuance of Approvable Letter

BACKGROUND: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, was resubmitted on February 12, 2002 (in response to a not approvable letter, dated November 27, 2000) for the following proposed indication: prevention of the symptoms of frequent heartburn for 24 hours. This application was discussed at the joint meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee on June 21, 2002. An

approvable letter was signed by Dr. Bull and Dr. Houn and faxed to the sponsor's agent, Proctor and Gamble, this morning prior to this teleconference.

**TODAY'S CALL:** Dr. Houn acknowledged that an approvable action was taken today and conveyed the following points to the sponsor:

1. FDA supports over-the-counter (OTC) use of omeprazole magnesium and encourages the sponsor to pursue approval of this drug product.
2. FDA acknowledges that obtaining uniform advice from different units within the agency can be problematic. Therefore, the Office of Drug Evaluation III, the Office of Drug Evaluation V, the Division of Gastrointestinal and Coagulation Drug Products, and the Division of Over-The-Counter Drug Products have worked together diligently to craft an approvable letter containing the best possible advice for further development and eventual approval of the OTC use of omeprazole magnesium.
3. The uses for omeprazole magnesium are not clearly stated in the proposed labeling ("*Uses*" section).
  - It was noted that in November 2001, prior to resubmission of the NDA, Proctor and Gamble engaged FDA in a discussion requesting that FDA accept a proposed 14-day treatment regimen \_\_\_\_\_ for \_\_\_\_\_ indication. This request resulted in three months of discussion with multiple experts that, in retrospect, did not help either the FDA or the sponsor with this issue other than to identify that the proposed "*Uses*" section of the labeling was problematic which was already known. FDA hopes to avoid this experience during the next review cycle.
  - The Joint Advisory Committee also felt that the proposed "*Uses*" section of the labeling was not ideal. Self-selection by consumers for use of this drug product was not demonstrated (the Joint Advisory Committee vote was 15-no and 3-yes for demonstration of self-selection).

FDA believes this outcome is the result of the confusing nature of the sponsor's proposed "*Uses*" section of the labeling. For example, does the prevention of frequent heartburn for 24 hours mean that a consumer will not experience heartburn for 24 hours after completion of the 14-day regimen? Or does it mean that the consumer will not experience heartburn for 24 hours while taking the drug product?

- FDA believes the submitted data support a treatment, not a prevention indication. The drug product does not provide primary prevention of heartburn as consumers must have the condition of frequent heartburn to appropriately self-select. The drug product does not provide secondary prevention of heartburn either because the data do not support that consumers avoid increased morbidity of frequent heartburn.
- The challenge for the sponsor is to state what the drug product does in the "*Uses*" section of the labeling (e.g., treatment of frequent of heartburn) and to clearly distinguish it from

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other uses such as immediate relief of heartburn or prevention of heartburn due to consuming certain foods or beverages.

- FDA asked whether there is some agreement between AstraZeneca and Proctor and Gamble that prohibits use of the term "treatment" or if there is some other concern that FDA should know to better advise the sponsor about the "Uses" section? (See "Discussion" below).
4. The revised draft labeling must be tested in a new labeling comprehension study and it must have a high rate of correct understanding.
- The sponsor may wish to test several versions of a statement and submit the best one based on the results of the testing. These types of comparisons will help convince FDA that the best statements have been selected and will minimize the sponsor's time and effort if a single statement tested does not do well.
  - The sponsor should submit revised labeling and a label comprehension study protocol to FDA for comment prior to initiation of the study.
5. FDA reiterated its support of omeprazole magnesium for OTC use. The advice provided in the approvable letter represents FDA's best collaborative view on how the sponsor can advance as quickly and smoothly as possible with certainty about FDA's position.

#### Discussion

##### **Issue 1: Prevention versus treatment:**

The sponsor conveyed the following points:

- Proctor and Gamble does not have an agreement, formal or informal, with AstraZeneca that prohibits use of the word "treatment."
- The sponsor may explore ways of testing the use concept with words other than "treatment."
- Prevention of heartburn is the endpoint in the pivotal clinical trials. There is no clinical data to support a treatment indication for frequent heartburn.
- The sponsor believes FDA has concluded that the appropriate indication for this drug product is treatment of frequent heartburn because "treatment" implies that there is an active condition for which the drug product provides an intervention. However, 73% of consumers tested said that taking the drug product every day for heartburn several days per week is "preventing heartburn." Consumers do not consider frequent heartburn a condition to be treated because it is episodic. Therefore, the word "treatment" does not convey a clear concept to consumers.

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FDA conveyed the following points:

- The Joint Advisory Committee concluded by a vote of 15 to 3 that appropriate self-selection by consumers was not demonstrated. The Committee was unanimous about the ambiguity of the proposed "Uses" section of the proposed labeling.
- FDA has considered at length the concept of "prevention" and how consumers understand that concept. This issue can be discussed further with the sponsor in an end-of-review meeting.
- FDA will consider the sponsor's proposals for alternative wording to convey the appropriate use of the drug. However, the best advice is to use language that conveys the concept that the product is for the use of treatment of frequent heartburn. This advice represents the collaborative view of both Offices and Divisions and will likely ensure the quickest and most certain path to approval of the drug product.

**Issue 2: Time to action**

The sponsor asked FDA to share its thoughts on the following recommendation in the approvable letter regarding the "Uses" section of the labeling:

"This section of the label must reflect that omeprazole magnesium tablets may take 1 to 2 days of use to work."

FDA said the labeling should convey to consumers that the drug product will not treat an acute episode of heartburn and may take \_\_\_\_\_ days to work.

The sponsor said the data from the clinical trials demonstrate that the drug product has an effect in the first 24 hours for the prevention of heartburn. The consumer research data showed that consumers understand how to use the drug product as only 3% took the drug for less than 14 days. Therefore, the sponsor believes that to say the drug product takes \_\_\_\_\_ days to work is unfounded.

FDA said the underlying pharmacology (some acid suppression within 24 hours with greater effects in \_\_\_\_\_ days) reinforces that the drug product is not intended for the acute treatment of heartburn or the prevention of meal-induced heartburn as consumers need to take multiple doses for maximum effect. Therefore, FDA recommends that the label reflect that the drug product may take \_\_\_\_\_ days to work.

The sponsor said it agrees that the drug product is not intended for episodic heartburn but the data demonstrates that a significant number of consumers who took the drug for frequent heartburn reported no heartburn the first day. Therefore, to say that the drug product takes \_\_\_\_\_ days to work implies that there is no effect the first day.

FDA said the sponsor can test phrases such as "may take            days," "sometimes takes days," or other phrases. This issue can be addressed further with the sponsor at an end-of review meeting.

Action Items:

The sponsor will request an end-of review meeting to discuss the approvable letter in more detail.

Minutes Preparer: Maria R. Walsh

Chair Concurrence: Florence Houn  
Jonca Bull

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**DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**MEMORANDUM**

**DATE:** August 7, 2002

**FROM:** Jonca Bull MD, Director, ODE V

**TO:** File NDA 21-229  
Omeprazole Magnesium Tablets, 20 mg,  
Proctor and Gamble/Astra Zeneca

**SUBJECT:** NDA action

The submitted application is for the OTC switch of omeprazole magnesium 20mg tablets. As noted in Dr. Houn's memorandum, there have been extensive discussions including two advisory committee meetings, internal discussions with SGE's, as well by the review divisions. In order for a drug product to be exempt from the provisions under section 503(b)(1)(C), sufficient evidence must be provided for the protection of public health by reason of a drug's lack of toxicity or other potential harmful effects. Evidence must also be provided that demonstrates that the drug product can be used safely and effectively in self medication by consumers as directed in proposed labeling.

The sponsor has not provided labeling with adequate substantiation by comprehension studies to meet these conditions for this drug product and OTC usage.

There remain serious concerns regarding whether labeling can be developed for this product that adequately conveys to the consumer information to correctly self select, provides for the differentiation of use from similar OTC products for treatment of heartburn, as well as appropriately seeking professional help. Additional labeling comprehension studies which focus on the concepts articulated in the approvable letter must be done in order to resolve these issues.

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Jonca Bull  
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MEDICAL OFFICER

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## MEMORANDUM

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

DATE: August 6, 2002

FROM: Florence Houn MD MPH

SUBJECT: Office Director Memo

TO: NDA 21-229 Prilosec 1 (omeprazole magnesium) OTC 20mg tablets  
Procter and Gamble and AstraZeneca

This memo documents my concurrence to issue an approvable action letter to Procter and Gamble and AstraZeneca for their over-the-counter (OTC) marketing application for omeprazole magnesium 20mg tablets. This OTC proposal was first discussed in the October 2000 OTC-GI Drugs Advisory Committee meeting, when indications purporting immediate relief and prevention of heartburn brought on by consuming certain foods and beverages were rejected. Data did not show onset of action of the drug to support these claims. The manufacturers re-did the labeled indication to "prevention of the symptoms of frequent heartburn for 24 hours." The manufacturer contacted the GI and OTC divisions, ODE 5, and myself around November of 2001 asking to get FDA acceptance of a 14-day treatment course (instead of a 28 day course) and asking that we agree on the indication. This request triggered a series of FDA meetings with special government employees to obtain their views. It was clear that everyone had problems with the prevention indication as worded. The issue of 14 days or 28 days was left up to the review divisions once the entire application was submitted. During this review cycle, both the GI and review divisions discussed many issues relating to appropriate use, compliance with labeling, risks of undertreatment of GERD, risks of self-medication for a serious disorder, safety concerns of long-term exposure, and appropriate OTC labeling, especially the indications and directions. Another joint OTC-GI Drugs Advisory Committee was held on June 12, 2002. The committee voted that the sponsor had not demonstrated consumers could self-select for use of OTC omeprazole magnesium 20mg tablets (vote 15-no vs. 3-yes for demonstration of self-selection). The vote was 17-1 in favor of 14-day course of treatment. The vote was 16-2 in favor or approval for OTC use, but with unanimous recommendation that the labeling be revised extensively and retested for comprehension. To this end, the divisions of gastrointestinal drugs and over-the-counter drugs are proposing revised labeling and retesting for comprehension. The application is approvable pending those changes and a satisfactory comprehension study.

Safety

The advisory committee stated that GERD could be treated OTC. The committee decided seeking physicians advice was not the only appropriate course of action following a 14-day treatment failure or recurrence of symptoms of frequent heart burn. The committee stated concerns that the drug may mask symptoms of a serious disease (cancer) are diminished if the label lists warning signs such as weight loss and dysphagia. Concern about carcinogenesis was discussed and at this time the data did not support human risk of increased cancer other than ecological association from epidemiologic observation. Use of Prilosec in pregnancy as documented in registry data from Europe will result in labeling text changes that are reassuring about in utero exposure, but there will not be a pregnancy category change. Drug interaction data are not known for digoxin, so it will be contraindicated. Anti-fungal medications are all expected to increase levels of omeprazole, so the class, antifungal drugs, will be referred to, not just ketoconazole, in the label. The interaction with phenytoin was not felt by the committee to be clinically important. The committee recommended that brand names be used in the label to help consumers identify drug interactions. However, use of brand names would require frequent reprinting of the label as names are added and changed and use of brand names would devote a disproportional amount of space to this section. The committee encouraged use of omeprazole magnesium not be more than for 2-3 courses in a year, one

every 4-6 months. These recommended intervals of use helps guide patients to understand if they should be seeking medical advice because their symptoms are more frequent.

Many patients will not follow these instructions and some of these patients may have a serious disorder. However, early diagnosis for esophageal and upper-GI cancers may not improve survival or mortality, so not following the instruction may not affect clinical outcomes. Early diagnosis of chest pain from certain cardiac etiology could improve survival with correct therapy. There is little change from the current situation with the over-the-counter H-2 receptor antagonists (H2RA) also being subject to these concerns of delaying diagnosis of cardiac pain. One could hypothesize increased time interval for consumers to fail OTC medications and see a doctor if omeprazole magnesium 20mg tablets is added to the OTC options list, but many doctors now may have patients take a trial of prescription PPIs for frequent heartburn, also delaying cardiovascular diagnosis.

#### Efficacy

The Uses section contains the word "prevention." This is objectionable to me because prevention to many lay people means 100% avoidance of an event; not risk reduction. Furthermore, primary prevention is in those patients who are disease-free, not the intended use population for OTC omeprazole magnesium 20mg tablets, which has frequent heartburn. Secondary prevention is to decrease morbidity or prevent additional injury from the disease. This indication is also not appropriate for OTC omeprazole magnesium 20mg tablets.

The current labeling ("for the prevention of the symptoms of frequent heartburn for 24 hours") is redundant with "the symptoms of frequent heartburn" because heartburn is a symptom. The "for 24-hours" is unclear. Is the prevention for 24 hours if you take it for 14-days, meaning, one will not have heartburn for the whole day while on the drug? Or, does it mean after you finish the 14-day course, you will not have frequent heartburn for 24 hours following the end of the treatment course? Either way, the message is unintelligible. The course is 14 days to treat frequent heartburn, which could be caused by acid reflux. The efficacy data showed a sufficient response for 14-days in a proportion of patients. The company will be asked to write the indication section in a straight forward manner. It may turn out that various marketing agreements between the two manufacturers over the wording of the indication will make the Agency's and committee's desire for a clear label difficult, but the current state of the label is confusing, unintelligible, and unacceptable. The NDA sponsors will again be asked to come up with an adequate indication statement that reflects what the drug is intended to do and for whom.

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Florence Houn  
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MEDICAL OFFICER

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**From:** Raczkowski, Victor F  
**Sent:** Friday, July 19, 2002 9:56 AM  
**To:** Walsh, Maria R; Ellenberg, Walter  
**Cc:** Ganley, Charles J; Katzper, Linda; Bull, Jonca; Korvick, Joyce A; Houn, Florence; Raczkowski, Victor F  
**Subject:** Documentation of telephone discussion with Dr. Bierer  
The purpose of this e-mail is to document a phone conversation that I had with Dr. Douglas Bierer of Procter & Gamble on NDA21-229 for Prilosec 1 (omeprazole magnesium tablets).

Dr. Bierer called me yesterday to obtain information about whether the company is on the right track in its interpretation of the outcome of the June 21st joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee. Apparently the company has already begun revising the Drug Facts label and has done some surveys in anticipation of the need to perform label comprehension studies.

I told Dr. Bierer that my best recommendation would be for the company to wait until receipt of the action letter before finalizing its Drug Facts label and initiating studies. In response to his questions, I indicated that the advice given by the Joint Advisory Committee varied, and that even though FDA usually (but not always) follows the advice given to it by its Advisory Committees, sometimes FDA uses regulatory/scientific discretion.

Dr. Bierer then pressed me on specifics on FDA's evaluation of the Advisory Committee meeting, on which I declined to comment given that FDA is still working on finalizing its action. I indicated that in the action letter, FDA would likely be providing the company with recommendations of how to alter the Drug Facts label, but would likely not be providing the company with exact wording to use. I indicated that, instead, the company would need to take FDA's action letter and recommendations, propose new language for the label, and then evaluate the new Drug Facts label in labeling comprehension studies. He then provided a detailed, long list of the company's interpretation of the Advisory Committee's recommendations, to which I provided no comment.

Dr. Bierer questioned who at FDA has been making the decisions about how to proceed after the Advisory Committee, and I indicated that it was a cooperative effort between the Division of the Over-the-Counter Drug Products, the Division of Gastrointestinal Drug Products, and the respective Offices.

Dr. Bierer questioned whether FDA was still aiming for an action by the end of July (he cited a phone conversation he had with Dr. Ganley). I indicated that an action by the end of July might be possible, but that FDA certainly hoped to complete the action by the PDUFA goal date in mid August.

In response to his question, I indicated that FDA might have a brief (probably high-level) teleconference with the company prior to sending it the action letter, so that the company would have some idea of what to expect. He welcomed the opportunity for such a discussion, and also noted that two meetings between FDA and Procter & Gamble are already scheduled after the PDUFA goal date of August 12, 2002: one to discuss the action letter, and one to discuss the company's new proposals. He emphasized that the company wanted to resolve as many issues as possible before the resubmission, and I indicated FDA would work with the company on the issues.

Finally, he offered to send the company's perspectives on the outcome of the AC meeting, and I said that it would be fine for the company to do so.

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Victor Raczkowski  
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MEDICAL OFFICER  
Documentation of phone conversation with Dr. Bierer

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## MEMORANDUM OF TELECON

DATE: June 27, 2002

APPLICATION NUMBER: NDA 21-229: Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Linda Jones, Regulatory Affairs  
Phone: (513) 622-3176  
Representing: Proctor and Gamble Company

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-229: Prilosec 1 (omeprazole magnesium) Tablets  
Label Comprehension Study

**BACKGROUND:** NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, was resubmitted on February 12, 2002 (in response to the not approvable letter dated November 27, 2000) with the following over-the-counter (OTC) indication: the prevention of the symptoms of frequent heartburn. A joint meeting of the Gastrointestinal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee was held on June 21, 2002. The action due date for this application is August 12, 2002.

In a telephone conversation yesterday (see Memorandum Of Telecon, dated June 26, 2002), Linda Jones asked me whether the Agency would request a "full blown" label comprehension study including all the various cohorts in the approvable letter. I told her I couldn't answer that at that time.

**TODAY'S CALL:** I called Ms. Jones and asked her to elaborate on the sponsor's plan for a new label comprehension study. She said the sponsor is considering eliminating from testing some cohorts such as the drug-drug interaction cohort and the pregnancy/nursing cohort. She said the sponsor is also considering targeting specific parts of the label rather than the entire Drug Facts label.

After conferring with Karen Lechter, J.D., Ph.D., Social Science Analyst, Office of Drug Safety, I called Ms. Jones and relayed the following advice: The Agency would need to see the study protocol and the revised label before deciding whether a shorter version of the study is appropriate. We would advise, at this preliminary point, that all cohorts tested in Study 02255 should also be tested in the new study with the possible exception of pregnant and nursing women. In addition, because something that may have been well understood in the label already tested may not be as well understood when the label is revised, we believe the entire Drug Facts label should be tested in the new study. I again emphasized that final recommendations would be forthcoming once the revised label and study protocol are submitted.

The call was then concluded.

/s/

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Maria R. Walsh, M.S.  
Regulatory Project Manager

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Maria Walsh  
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## MEMORANDUM OF TELECON

DATE: June 26, 2002

APPLICATION NUMBER: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Linda Jones, Regulatory Affairs  
Phone: (513) 622-3176  
Representing: Proctor and Gamble Company

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-229: Prilosec 1 (omeprazole magnesium) Tablets  
Pending regulatory action

**BACKGROUND:** NDA 21-229, Prilosec 1, (omeprazole magnesium) Tablets, was resubmitted on February 12, 2002 (in response to the not approvable letter dated November 27, 2000) with the following over-the-counter (OTC) indication: the prevention of the symptoms of frequent heartburn. A joint meeting of the Gastrointestinal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee was held on June 21, 2002. The action due date for this application is August 12, 2002.

**TODAY'S CALL:** Linda Jones called me for information about how the Agency plans to proceed regarding the pending regulatory action. I told her we are reviewing the recommendations of the joint Advisory Committees regarding the labeling and we plan to issue an approvable letter listing all the issues the sponsor must address before the drug may be approved. The letter will include our recommendations for revising the labeling.

Ms. Jones asked if a label comprehension study would be required. I replied that the Agency is considering the recommendation by the Joint Advisory Committees that the sponsor conduct a label comprehension study and would most likely request that this study be conducted. Ms. Jones asked whether the label comprehension study would need to be a "full blown" one including all the various cohorts. I told her I couldn't answer that at this time.

Ms. Jones asked if there would be an opportunity for the sponsor to discuss the labeling with the Agency. I replied that we were not heading in the direction of hammering out a specific label that could be agreed upon in this review cycle. Rather, we would provide recommendations for revising the labeling and the sponsor could then submit revised labeling to the IND for our consideration after the action letter issues. She said the sponsor could submit a revised label and conduct some consumer surveys and submit that data to us in this review cycle. I replied that we would probably not be reviewing any additional data in this review cycle but that a revised label

NDA 21-229

Page 2

could be submitted and we might consider it in formulating our recommendations for labeling revisions in the action letter.

The call was then concluded.

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Maria R. Walsh, M.S.  
Regulatory Project Manager

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Maria Walsh  
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**MEMORANDUM OF TELECON**

**DATE:** late June, 2002, probably shortly after the advisory committee meeting of June 21.

**APPLICATION NUMBER:** NDA 21-229: Prilosec1 (omeprazole magnesium) Tablets

**BETWEEN:**

**Name:** unknown

**Phone:** unknown

**Representing:** Proctor and Gamble Company

**AND**

**Name:** Karen Lechter, J.D., Ph.D., Social Science Analyst

**Division of Surveillance, Research, and Communication Support,  
HFD-410**

**SUBJECT:** NDA 21-229: Prilosec 1 (omeprazole magnesium) Tablets  
Label Comprehension Study

**CONTENT OF DISCUSSION:** This memorandum is being prepared at the request of the HFD-180 project manager for this product to summarize a conversation about which no notes were taken by FDA staff at the time of the call. To the best of my recall, a representative of the sponsor called to ask about the methodology for comparing two versions of the product label. After a short conversation, I told him that the methodology would depend on what they were trying to study, and I could not give them a definitive answer. I believe I indicated that it may not be necessary to compare two versions of the label, but that the review division may have some preferences in that regard. One label might be sufficient. I indicated that they would receive a letter from the FDA that might address label comprehension issues.

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Karen Lechter .  
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Toni Piazza Hepp  
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PHARMACIST

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** June 5, 2002  
**Time:** 11:00 a.m. - 12:00 p.m.  
**Location:** Parklawn Building, Potomac Conference Room

**Application:** NDA 21-229  
Prilosec 1 (omeprazole magnesium) Tablets

**Sponsor:** AstraZeneca, LP/The Proctor and Gamble Company

**Type of Meeting:** Pre-Advisory Committee Meeting

**Meeting Chair:** Victor Raczowski, M.D., Acting Division Director, HFD-180  
**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### FDA Attendees:

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczowski, M.D., Acting Director  
Joyce Korvick, M.D., Deputy Director  
Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader  
Mark Avigan, M.D., Medical Officer  
Maria R. Walsh, Regulatory Project Manager

#### Division of Over-The-Counter Drug Products (HFD-560)

Linda Katz, M.D., Deputy Director  
Daiva Shetty, M.D., Medical Officer  
Mary S. Robinson, Interdisciplinary Scientist/Chemist  
Helen Cothran, Interdisciplinary Scientist/Chemist  
M. Atiar Rahman, Ph.D., Statistical Reviewer  
David Hilfiker, Chief, Project Management Staff  
Walter Ellenberg, Regulatory Project Manager

#### Advisors and Consultants Staff

Sandra Titus, Ph.D., Executive Secretary, NDAC

### Sponsor Attendees:

#### AstraZeneca, LP

Doug Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs  
George Kummeth, Associate Director, Regulatory Affairs

#### The Proctor and Gamble Company

Robert Greene, VP Personal Health Care R&D  
Keith C. Triebwasser, Ph.D., Senior Director, Regulatory Affairs  
Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs

**Background:** NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, was resubmitted on February 12, 2002 (in response to a not approvable letter, dated November 27, 2000) for the following proposed indication: prevention of the symptoms of frequent heartburn for 24 hours. A joint meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee is scheduled on June 21, 2002 to discuss this application.

The Proctor and Gamble Company submitted a pre-meeting briefing package, dated May 14, 2002, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for today's meeting. The package included a list of three questions for discussion.

**Meeting Objective:** To discuss the sponsor's questions regarding the issues to be discussed at the joint meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee.

**Agenda Items:**

1. Based on your review of our NDA resubmission, what are your overall conclusions? What, if any, questions remain unanswered?
2. Based on your review, on what issues does the Agency plan to ask the Advisory Committee for guidance?

FDA Responses to Questions 1 and 2:

FDA has not yet reached an overall conclusion on the NDA.

FDA plans to ask the Advisory Committee for guidance on issues such as the following:

- Is the target population, people who have frequent heartburn, distinguishable from a population with gastroesophageal reflux disease (GERD) based upon the characteristics of those who self-selected Prilosec 1 in the actual use study? FDA noted that the majority of treated subjects had recurrence of heartburn within 3 months after discontinuation of treatment and only a small percentage consulted a physician.
- The proposed labeling states, \_\_\_\_\_ The majority of subjects who used the drug in the actual use study had heartburn symptoms for more than 3 months. However, only less than half consulted their physician within the last year and about one-third did not consult their physician at all. Is this compliance rate with the proposed labeling instruction acceptable?

- Does the actual use study (3 months duration) provide sufficient information to address a long-term intermittent usage pattern?
3. Are we addressing all of the data and issues that need to be discussed at the Advisory Committee meeting? Attachment II provides a draft outline of our Advisory Committee presentation.

FDA Response:

Attachment II addresses the data and issues that need to be discussed at the Advisory Committee meeting. Additional issues that should be addressed are outlined in our response to questions 1 and 2 above.

Discussion:

- Safety issues: The sponsor asked if FDA would have questions for the Joint Advisory Committee about the safety of Prilosec 1. FDA said safety issues were discussed at length at the previous meeting of the Joint Advisory Committee on October 20, 2000. There will not be a separate presentation of safety issues at the June 21, 2002 meeting of the Joint Advisory Committee. However, FDA is concerned about the long-term safety implications of the potential chronic intermittent use of Prilosec 1.
- Chronic intermittent use: The sponsor asked FDA to expound on its concerns about possible episodic use by consumers. FDA said the currently proposed label advises consumers to see a physician if heartburn continues or returns after one 14-day course. However, some consumers who have heartburn on a chronic intermittent basis may take the drug product in a cyclic fashion. FDA has the following questions regarding this issue: Is Prilosec 1 appropriate for use in consumers who have recurrent heartburn rather than episodic heartburn in an over-the-counter (OTC) setting? Do the actual use studies provide appropriate information about cyclic use of this drug product in these consumers? What is the impact on the safety of chronic intermittent usage?

The sponsor plans to address this issue at the Joint Advisory Committee meeting. The sponsor acknowledged that some consumers would not see a physician if heartburn continues after one 14-day course and plans to conduct a benefit/risk analysis of these consumers. The sponsor noted that one 14-day course is the recommended usage and cyclic use is an unintended consequence.

- Length of Therapy: FDA said the issue of appropriate length of therapy for frequent heartburn might arise at the Joint Advisory Committee meeting. Consumers with frequent heartburn may have GERD. The length of therapy for symptomatic GERD with the prescription formulation of Prilosec is 4 to 6 weeks. FDA has the following question

regarding this issue: If Prilosec 1 provides an alternative treatment for consumers with frequent heartburn/symptomatic GERD, is the proposed 14-day course the appropriate length of therapy for these consumers?

- **Labeling:** The sponsor asked if FDA would have specific questions for the Joint Advisory Committee about the proposed language in the labeling. FDA said it does not plan to ask the Joint Advisory Committee for specific recommendations on the language in the proposed labeling in a line-by-line fashion. Rather, FDA will ask the Joint Committee for general recommendations on whether the proposed labeling conveys the appropriate information adequately and if not, how it could be remedied.
- **Compliance:** The sponsor asked about FDA's determination of the adequacy of compliance data regarding the proposed labeling, i.e. what compliance rate is considered adequate? FDA said it does not consider a specific compliance rate as adequate for all drug products. Because drug products differ in their risk/benefit ratios, different compliance rates would be considered adequate for different drug products. FDA plans to present the compliance data for Prilosec 1 to the Joint Advisory Committee and ask for its opinion.
- **Pregnancy Category C:** It was noted that the prescription formulation of Prilosec is labeled as Pregnancy Category C. The sponsor asked how this issue will impact on the Prilosec 1 application and how it will be handled at the meeting of the Joint Advisory Committee. FDA said it does not plan to discuss this issue at the meeting of the Joint Advisory Committee. \_\_\_\_\_ FDA pointed out that the regulations addressing pregnancy for OTC drug products (21 CFR 201.63) do not specify pregnancy categories for OTC labeling.
- **Miscellaneous:** The sponsor inquired about the consultants attending the meeting of the Joint Committee and the speakers for the open public hearing. FDA said three voting consultants would attend the meeting, namely, Drs. Eric Brass, Edwin Gilliam, and Richard Neill. Three speakers will address the Joint Committee during the open-public hearing including Dr. Michael Wolfe, who has recused himself as chairman of the Gastrointestinal Drugs Advisory Committee. Dr. Louis Cantilena will chair the meeting.

FDA discussed the tentative meeting agenda and will provide the sponsor with a written copy of the draft agenda later this week.

If the questions have been finalized, FDA will provide the sponsor with a written copy of the final questions for the Joint Committee a few days before the meeting.

Meeting Minutes  
Page 5

Minutes Preparer:

Chair Concurrence:

Drafted: M. Walsh 7/29/02  
Initialed by: C. Ganley 8/14/02  
              V. Raczkowski 8/30/02  
Final: M. Walsh 9/3/02

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JUN 5 2002

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Date: May 23, 2002

From: OTC Omeprazole Magnesium (Prilosec 1™) Review Team

To: Gastrointestinal and Nonprescription Drug Advisory Committee Members, Consultants and Guests

Through: Division of Gastrointestinal and Coagulation Drug Products  
Division of Over-the-Counter Drug Products

Subject: NDA: 21-229: Prilosec 1 (omeprazole magnesium) for OTC Use

**Background**

Omeprazole, a proton-pump inhibitor, was approved for prescription use in 1989 and is currently marketed for the following indications:

- For the treatment of duodenal and gastric ulcer;
- For the treatment of gastroesophageal reflux disease (GERD);
- For the maintenance of healing of erosive gastritis;
- For the long-term treatment of pathological hypersecretory conditions.

The recommended dose and treatment duration range from 20 mg daily for up to 4 weeks for short-term symptomatic GERD to 20 mg daily for up to 12 months (for maintenance of healing of erosive esophagitis).

Currently there are two classes of drug products available OTC for use in heartburn: antacids and acid reducers also known as histamine-2 receptor antagonists (H2AR). Both of these classes of drugs are indicated for the treatment of acute occasional heartburn symptoms. The acid reducers have the additional claim for the prevention of meal-induced heartburn at specified times depending upon the product. The 24-hour prevention claim is one not currently available in the OTC market.

The switch of Prilosec from Rx to OTC was previously discussed on October 20, 2000 at a joint advisory committee composed of individuals from the two committees represented today. Originally, the sponsor sought to market Prilosec 1 OTC for the same indications for which OTC antacids and OTC H2-receptor antagonists are approved: "relief of heartburn, acid indigestion and sour stomach; and prevention of these symptoms brought on by consuming certain foods and beverages; and the prevention of symptoms for 24 hours." During that meeting efficacy, safety, pharmacokinetic issues, and consumers' ability to understand and use the product correctly without a learned intermediary were discussed. The Committees felt that adequate data had not been presented to support these indications for Prilosec OTC and approval was not recommended. However, the Committee indicated that the safety profile was such that Prilosec could be switched OTC if a suitable population could be identified that could use this product safely and effectively.

Based on the committee opinion, as well as subsequent discussions with the Agency, the sponsor submitted their completed response to the Agency in February 2002. In that response, the sponsor stated that the target OTC population is those suffering from "frequent heartburn. As such they modified the indication to: "for the prevention of frequent heartburn," "intended for those who suffer heartburn two or more days a week." In addition, they proposed modified versions of the directions for use. In support of these modifications, the sponsor submitted data obtained from an actual use and two label comprehension trials to address appropriate selection/deselection, expectation of benefits, and how this product would fit into the armamentarium of OTC "heartburn" therapy. In addition, to support the proposed 20.6 mg omeprazole magnesium dose, the sponsor relied on pharmacodynamic data showing more consistent acid

suppression at 20 mg than at 10 mg and that 20 mg provided a directionally higher level of prevention across all temporal variables than 10 mg, which was the dose previously proposed for OTC use. This data was discussed at the advisory committee meeting in October 2000. Further, the proposed 14-day duration of consecutive daily doses is proposed based on the efficacy data from the OTC trials and from the Actual Use trials.

#### **FDA Reviews**

##### *24-h Prevention: Results of Studies 171 and 183*

These studies were randomized; double blind, multicenter, and placebo-controlled trials to assess the efficacy of Prilosec 10mg and 20mg OTC in the prevention of further heartburn episodes. Entry criteria consisted of having heartburn of greater than 1-month duration, with a frequency of at least 2 heartburn episodes per week. An antacid or OTC H2RA responsive population was recruited. The results of the primary efficacy variable, the proportion of subjects with no heartburn over 24h, and at 14 days (secondary variable) are as follows:

- A substantial proportion of subjects experienced no heartburn on Day 1 or Day 14 in the placebo group.
- The therapeutic gain with Prilosec, although statistical significant, is only modest on Day 1.
- The therapeutic gain increases on Day 14, confirming that the maximum benefit of treatment relies on consecutive dosing.
- Approximately 30% of participants experience "breakthrough" heartburn on Day 14. This is defined as having an episode of heartburn despite using the medication according to directions.
- The proportion of responders is higher in subjects with low frequency heartburn at baseline versus high frequency; although the therapeutic gain is small.
- There is approximately a 40% treatment failure rate after 14 Days in subjects with high frequency heartburn at baseline, with the benefit being lost within 3 days of discontinuation of therapy.

##### *Biopharm Issues*

The pharmacokinetic profile of Prilosec is useful in understanding its efficacy. The half-life of omeprazole is short, 0.5-1 hour. There is also a slow pharmacodynamic onset, with acid inhibition only 50% of maximum at 24 hours, and a long-acting pharmacodynamic effect of acid secretion reduction to baseline over 3-5 days. It is these effects that make Prilosec ineffective in acute relief and make it beneficial for 24-hour prevention.

With regard to drug-drug interactions, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, R-warfarin, and tolbutamide. These effects may be clinically significant in susceptible individuals, such as those having liver disease. Thus, caution, in general, needs to be exercised when co-administering the above drugs with omeprazole.

##### *Safety*

The frequency of adverse events (AE) reported in the clinical trials were similar to those known for the prescription products, with regard to headaches (5%), infection (2%), and diarrhea (2%), without dose-related differences. The frequency of AEs reported in the Actual Use study was similar: headache (17.9%), diarrhea (3.8%), and abdominal pain (3.2%). Most of these reactions were not dose-dependent, and were transient in nature. The Safety Update did not reveal any new safety areas of concern.

##### *Actual Use Trial (#007)*

This was a multi-site, multi-dose, open-label, observational study of OTC consumers ("all-comers"), conducted in 5 different cities in the United States. Potential subjects were recruited from a variety of advertising media. The objectives of this study were to determine:

- The percentage of subjects who correctly self-selected that the study medication was a drug that they could or could not use;
- The percentage of doses where no more than one tablet of study medication was taken per dose;
- The percentage of dosing days where no more than one dose and no more than one tablet of study medication was taken per day;
- The percentage of subjects who took between 11-14 doses of study medication in an 11-17 day period (80-120% of dosing directions).

A total of 1301 consumers participated in the self-selection portion of the study. Of those, 1251 (96%) stated that Prilosec 1 was appropriate for them to use and 863 agreed to participate in the study. Of these, 854 purchased the study medication; 782 completed the study; and 758 actually purchased and used the drug. Overall, 83% of the primary population (those treating themselves with the drug) and 76% of the secondary population (those making a determination that the drug was appropriate to use) correctly self-selected. (Of note, the primary population is composed of people who had gone through 2 screening processes; whereas, the secondary population had undergone only one screening process.) Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. In addition, 13.5% of the self-selection (secondary) and 9% of the treated (primary) population who had infrequent heartburn ( $\leq 1$  day a week) and 8.2% has contraindicated conditions, classifying them as inappropriately self-selecting. Overall, compliance with the three-labeled directions (take 1 tablet a day, every day for 14 days) was achieved by 63% of the treated population. Compliance increased to 79% if the sponsor analyzed compliance as subjects taking between 11 to 14 doses of study medication in an 11-17 day period. Three percent exceeded 14 consecutive days of treatment and 33% took the drug for less than 14 days. The study showed that the majority of those using Prilosec 1 have long-standing heartburn. However, only 48% of those had spoken to their physician within the last year, and 35% had not spoken to a health care provider at all. The responses to the follow-up questionnaire (3 months after the study) showed that 58% of the consumers available for follow-up had their heartburn return; 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

#### *Pregnancy Category*

Pregnancy Category C is the recommended designation; based on the effects on the human fetus, especially developmental and behavioral, which have not been adequately defined. Based on the mechanism of action of the drug and the consistent results amongst several animal species, exposure to pregnant women should be limited.

#### *Labeling Comprehension*

Two label comprehension trials were undertaken to address the issue of whether consumers could understand the distinction between Prilosec 1 and the currently marketed antacids and H2RA. Of note, the labels used in both studies were not the same as the one used in the Actual Use Study, as these studies were conducted simultaneously. However, the label used in the Actual Use trial was similar to those being tested in the label comprehension trials.

Study 2255 suggests that the tested label does not adequately convey to consumers that the product is not for episodic use and that it is only for prevention. Further, the study also indicates that many who may choose to take this product are also using contraindicated medications or have contraindicated conditions, and may not check with a health care provider prior to taking Prilosec 1.

Study 12179 was conducted among persons who should consult a physician before using Prilosec 1 due to medical conditions. The results suggest that most people who should consult a physician before using the product may not understand that they should do so. Among participants, there was a good understanding of the use for frequent heartburn, but a low demonstration of understanding that the use is limited to prevention. After the study, the label was not substantially changed to improve the understanding in these areas.

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### Discussion

There are some very specific issues that need to be addressed in considering the safe and effective use of Prilosec 1 in the OTC setting. Despite a relatively short half-life of 2 hours, the pharmacodynamic effect can be measured for 3-5 days after initial administration. The mechanism of action, which has been described as an irreversible inhibition of the proton pump, has a half-life of 50 hours. These characteristics make the product less effective for relieving acute heartburn pain. However, the prolonged pump inhibition that makes this a successful product for repeated (chronic) administration, which is consistent with the new indication sought.

In light of the pharmacological characteristics of omeprazole, one of the questions to be addressed by the sponsor was whether consumers will accurately self-select for (or against) the prevention of frequent heartburn occurring two or more times per week. Overall, the Actual Use study showed that 76% correctly self-selected that the product was appropriate for them to use. This percentage is based on initial self-selection after picking up the product and reading the label. The percentage of correctly self-selecting is higher (83%) if the population that actually self-selected to participate and use the product is used. The majority of those enrolled (87%) and the majority of those treated (91%) had frequent heartburn as defined by having  $\geq 2$  episodes per week. Thus, the self-selection rate was better in those who actually chose to use the product.

The data from the Actual Use study also showed that the majority (98%) of those using Prilosec 1 had heartburn symptoms for more than 3 months; 48% of those had spoken with their physician or health care provider within the past year; and 35% had not spoken to a health care provider about their heartburn ever. This raises an issue that, if available OTC, consumers might not appropriately follow-up with a health care practitioner to identify and treat their underlying condition and may, simply choose to continue treatment chronically if symptomatic relief is afforded. The Actual Use study did not assess the issue of long-term chronic use without physician intervention as a measure of compliance with the directions.

As studied in the Actual Use trial, the duration of treatment for OTC use was 14 days of continuous use. The majority (97%) of the treated population did not exceed 14 consecutive days of therapy. Overall compliance with all three labeled directions: one tablet a day, every day, for 14 days, was achieved by 63% of the treated population. The difference in the percentages are due to the fact that: not all consumers took only one tablet of Prilosec 1 per dose, not all used just one tablet a day; or not all took medication continuously for 14 days. The responses to the 3-month follow-up questionnaire showed that 58% of the available participants had their heartburn return. Of these, 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

The label comprehension trials showed that approximately 80% of the participants understood that Prilosec 1 was for frequent heartburn. It was unclear from these studies, due to the way the questions were worded, if consumers understood that Prilosec 1 was intended for prevention only and not for acute or episodic relief.

An additional issue to be addressed is the consequences of long-term and/or chronic intermittent treatment without physician oversight and whether any of the more significant conditions may be masked as a result of consumers choosing to continue to medicate rather than follow-up with a health care provider. Given the targeted population for use (those with frequent heartburn), the issue remains as to whether the proposed duration of therapy (14 continuous days) should be influenced by the likelihood that patients with GERD (having a minimum duration of prescription therapy of 4 weeks) might purchase the medicine.

In summary, when reviewing the data presented in the briefing package consideration should be given to the following issues:

- Has the sponsor identified an acceptable target population?
- What is the appropriate duration of therapy?
- Has the sponsor demonstrated that consumers will see a physician for symptoms that fail to resolve and not self-medicate chronically without the benefit of a health care practitioner's advice?
- How should acute and episodic, as well as long-term intermittent use be addressed?

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**Review**  
**Division of Surveillance, Research, and Communication Support**

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>NDA #</b>                      | 21-229                              |
| <b>Drug:</b>                      | Omeprazole Magnesium Tablets        |
| <b>Sponsor:</b>                   | The Procter & Gamble Co.            |
| <b>Identification:</b>            | Label Comprehension Study 12179     |
| <b>Date of Reviewed Document:</b> | January 15, 2002                    |
| <b>Reviewer:</b>                  | Karen Lechter, J.D., Ph.D., HFD-410 |
| <b>Review Completed:</b>          | May 8, 2002                         |

**Overview**

This label comprehension study was conducted among persons who should consult a physician before using Prilosec 1 due to medical conditions. The results suggest that most persons who should consult a physician before using the product due to their medical conditions may not understand that they should do so.

The label used was similar to the final proposed label. However, it listed the same six medications used in the label for label Comprehension Study 2255 as reasons to ask a doctor before use, rather than the three medications used in the final proposed label.

Among participants, there was good understanding of the use for frequent heartburn, but low demonstration of understanding that the use is limited to prevention. After this study, the proposed label was not substantially changed to improve understanding in these areas.

**Communication Objectives**

The objective of this study was to evaluate whether consumers understand if they are appropriate candidates for using Prilosec 1 and whether they are required to ask a doctor before use, as identified in the Warnings section of the tested label.

**Methodology**

Participants

Participants were 145 males and females age 18 or older, who had frequent heartburn (two days or more a week) and had at least one contraindicated symptom listed in the warning section of the label. Forty (40) had only one symptom and 41 had more than one. All were pre-recruited using databases from market research data collection facilities. Participants were screened by telephone and were asked to come to a central location for the interview. None were taking warfarin, phenytonin, diazepam, clarithromycin, itraconazole, or ketoconazole, which were mentioned on the tested label as contraindicated. In the past month, they experienced one or more of the following:

- chest pain
- chest pain with any of the following:
  - shortness of breath

- sweating
- pain spreading to arms neck or shoulders
- lightheadedness
- trouble swallowing food
- wheezing
- wheezing with heartburn
- unexplained weight loss

During the study, chest pain and wheezing were categorized as infrequent or frequent to determine appropriate self-selection, as the label said those with frequent chest pain or frequent wheezing should consult a doctor before use. Participants were not asked if they now take or ever took Prilosec.

### Procedure

Interviews were in five geographically dispersed markets in the United States. After arrival at the research facility, participants were re-screened for qualifications. They were given the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy test and categorized as literate or low literate (reading level 8<sup>th</sup> grade or below).

The label used was similar to the final proposed label. However, it listed the same six medications used in the label for label Comprehension Study 2255 as reasons to ask a doctor before use, rather than the three medications used in the final proposed label. The use section of the tested label stated "For prevention of frequent heartburn," like the earlier label comprehension study label, and unlike the proposed label that says "for prevention of the symptoms of frequent heartburn for 24 hours."

Participants examined a Prilosec 1 label as if they were in a store thinking about whether or not to purchase it for their own personal use. After examining the label, they were told "we want to make sure that people are able to understand if they can use the product and how to use the product in a safe and effective manner."

Participants were asked what the product is used for. After this question, they were told "As you may or may not have stated, this product is used for the prevention of frequent heartburn—only for those people who get heartburn two or more days a week." Then they were asked whether they could personally use Prilosec 1 immediately and why they responded as they did (Q.2-3). If their reason for their response did not relate to the label information, they were asked again to

assume that this is a product you want to use, but you just need to determine whether it is intended for you, personally, to use it....  
Considering everything on the package label, is the product intended for you, personally to take home and start using *immediately*?

They were asked why they responded as they did. (Q.4-5).

Next, they were asked whether persons with contraindicated symptoms in hypothetical scenarios could use the product. For the scenarios, they were asked to pretend they were the person described. The contraindicated symptoms in the scenarios included frequent chest pain, chest pain with shortness of breath, pain spreading to the arms, and frequent wheezing, particularly with heartburn. Participants were asked for their medical history relating to contraindicated symptoms. They were asked if they noticed the contraindicated symptom warning section on the label and what that section of the labeling was telling them. For those who indicated they would use the product, they were asked the reasons they felt the product was intended for their use.

## Results

### Self-selection

The critical question in this study was the self-selection one. Participants, all of whom had some degree of symptoms listed on the label as requiring consultation with a physician, stated whether or not the product is intended for them personally to take home and start using immediately.

Participants were considered by the sponsor to have successfully met the objective if their response to the self-selection question was correct or acceptable. Correct responses were correct on the first response according to the label information or after a follow-up probe. Acceptable responses were those that were not according to the label, but would not have resulted in incorrect use, such as consulting a doctor.

For the self-selection question, the 145 participants were categorized based on responses to the personal history questions as:

1. **Infrequent Symptom (N=39).** This group had chest pain or wheezing that was not frequent and, therefore, not considered one of the symptoms listed in the warning section of the label. (The label refers to "frequent chest pain" and "frequent wheezing, particularly with heartburn.") These participants were considered "okay to use" the product.
2. **Symptom Reported to Healthcare Provider (N=50).** Those who had a symptom listed in the warning section of the label but who had reported the symptom to a healthcare provider were considered "okay to use" the product by the sponsor. There was no time period specified for reporting. The Agency believes that these participants should not have been categorized as "okay to use." This issue is discussed in more depth later in this review.
3. **Not Reported Symptom to Healthcare Provider (N=56).** Those who had a symptom listed in the warning section of the label but had not reported it to a healthcare provider should "ask their doctor first" before using the product.

Each response to the self-selection question and the self-reported medical history was reviewed to determine if the response was "correct," "acceptable," or "incorrect" by comparing the self-selection answer with one of the three categories described above.

As described earlier, the sponsor deemed that persons were appropriate to use the product if they had reported their contraindicated symptoms to a health care provider in the past or if they had infrequent wheezing or chest pain.

The sponsor's classification resulted in 38% (N=56) who should have answered the question by saying they should ask a doctor before use. An additional thirty-four percent (34%) had reported symptoms to the health care provider, and 27% had infrequent symptoms. These last two groups were scored correct if they answered that it was appropriate for them to use the product.

Based on the sponsor's analysis, 81% had a correct self-selection response. However, half (28/56) of participants who had not reported their contraindicated condition to a health care provider said they would use the product. Thus, 50% of this group responded incorrectly, 50% correctly.

Table 1. Sponsor's Classification of Medical History Compared to Consumer Response to the Self-Selection Question Among All Participants

| Responses by Consumer Category                                        | N          | %<br>(base=145) |
|-----------------------------------------------------------------------|------------|-----------------|
| <b>Correct/Acceptable Self-Selection (total)</b>                      | <b>117</b> | <b>81</b>       |
| Symptom(s) reported to healthcare provider (HCP) (OK to use)          | 50         | 34              |
| Infrequent symptom (chest pain and/or wheezing) (OK to use)           | 39         | 27              |
| Consumer had not reported symptoms to HCP but indicated he/she would  |            |                 |
| • ask a doctor (not OK to use)                                        | 16         | 12              |
| • not use it (not OK to use)                                          | 9          | 6               |
| • use it, but already taking Prilosec (acceptable)                    | 2          | 1               |
| • use it, but had reported symptom to pharmacist (acceptable)         | 1          | 1               |
| <b>Incorrect Self-selection (Total)</b>                               | <b>28</b>  | <b>19</b>       |
| Consumer had not reported symptom(s) to HCP and would use the product | 28         | 19              |
| <b>Total</b>                                                          | <b>145</b> | <b>100</b>      |

The Agency performed additional analyses on the self-selection findings. We eliminated those who, according to the label, need not ask a physician before use or who were taking Prilosec (Q.2). Because some participants (39) had infrequent chest pain and wheezing, they were not required to consult a physician before using the product. Two others were already taking Prilosec. These 41 should not have been counted in the base. If we eliminate those 41, we are left with a sample of 104 who should not use the product without contacting a physician.

The Agency also reclassified those who have discussed their contraindicated condition with the doctor in the past. We classified them as not appropriate for use because there is no evidence they ever discussed Prilosec with a health care provider. They should not

have said Prilosec 1 was appropriate for their use. We considered the person who spoke with a pharmacist about his or her condition as not appropriate for use.

Q.2 states the following:

Now we need you to decide whether this product is intended for you, **personally**, to use. In other words, please think about yourself and whether this product is right for you or not. To do this, please assume you are at the store and you've just picked up this package. Considering everything on the package label, is this product intended for you, **personally**, to take home and start using *immediately*?

Based on answers to Q.2, of the 104\* remaining, all of whom should ask a doctor before use, 27 (26%) would ask a healthcare provider before use and 20 (19%) would not use it, for a total of 45%. These were the only ones to respond correctly according to the label. Fifty-three percent (53%) were incorrect; they said the product was appropriate for them to use. These data suggest that many who should have avoided the product or should have contacted a doctor first due to their medical conditions are not using these conditions as a basis for their decisions about using the product.

The following table reflects the Agency analysis of the results. Overall most (53%) selected **incorrectly** in response to Q.2.

Table 2. FDA's Classification of Responses of Participants Who Should Contact a Physician Before Use, Based on Responses to Q.2.

| Responses by Consumer Category                   | N         | %<br>(base=105) |
|--------------------------------------------------|-----------|-----------------|
| <b>Correct/Acceptable Self-Selection (total)</b> | <b>47</b> | <b>45</b>       |
| Ask a doctor                                     | 27        | 26              |
| Would not use                                    | 20        | 19              |
| <b>Incorrect Self-Selection—would use</b>        | <b>56</b> | <b>53</b>       |

Q.4 asked those who gave non-label reasons for their response to Q.2 if they can tell by the way the package label is written if they personally can use the product. These results are based on 19 participants. Five (5) of these can be eliminated from the base because they had infrequent wheezing or infrequent chest pain. Of the remaining 14, 11 said "OK to use," and 3 said they would consult a doctor first. Therefore, 79% of this small group was incorrect.

#### Product Purpose

Thirty-two percent (32%) of the total sample of 145 correctly stated that the product is for prevention of frequent heartburn. Sixty-eight percent (68%) gave a partially correct

\* The sponsor's results did not identify where one of the Prilosec users was reported in the data listings for Q.2. Therefore, that person could not be eliminated from this re-analysis and the base is 105 participants.

response, such as heartburn (34%), prevent heartburn (9%), frequent heartburn (17%), or acid reducer (8%).

**Table 3. Correct and Partially Correct Responses About Product Purpose**

| Response                   | N         | %<br>(base=145) |
|----------------------------|-----------|-----------------|
| <b>Totally Correct:</b>    |           |                 |
| Prevent frequent heartburn | 47        | 32              |
| <b>Partially Correct:</b>  | <b>98</b> | <b>68</b>       |
| Heartburn                  | 49        | 34              |
| Prevent heartburn          | 13        | 9               |
| Frequent heartburn         | 24        | 17              |
| Acid reducer               | 12        | 8               |

Those 74 who said to prevent heartburn, for heartburn, or an acid reducer, but not those who said frequent heartburn, were asked if the product is for a specific type of heartburn. Forty-nine (49; 66%) of those answered yes. Forty-two (42; 57%) of the 74 who were asked if it is a specific type responded that it is for frequent heartburn. Thus, the total stating that it is for frequent heartburn (either to prevent frequent heartburn, frequent heartburn, or for frequent heartburn after follow-up questioning) is 113 (47+24+42), which is 78% of the initial group of 145.

**Table 4. Responses About Purpose After Initial and Follow-up Questioning**

| Response           | N  | %<br>(base=145) |
|--------------------|----|-----------------|
| Frequent heartburn | 42 | 29              |
| Heartburn          | 49 | 34              |
| Prevent heartburn  | 13 | 9               |
| Acid reducer       | 12 | 8               |

From these responses, we can conclude that most participants understood Prilosec 1 is for heartburn. About 80% understood it is for frequent heartburn. About 40% mentioned prevention in their responses. It is possible that there would have been a higher score for prevention if there had been a follow up question that would have focused on that issue, as there was for the type of heartburn. However, as there was no such follow-up question, we do not know how well prevention was part of the concept the participants had about the drug. There were no questions specifically on that issue in the study.

#### Scenario Questions

Four hypothetical scenario questions asked whether persons with certain health conditions could use the product. Three of these conditions were on the label—(1) chest pain spreading to your arms, and shortness of breath; (2) frequently wheeze, particularly

with heartburn; and (3) frequent chest pain. The second question in this series asked about headache, which is not mentioned on the label. For the conditions mentioned on the label, scores were high. Interestingly, for the question about headache, 66% correctly said the person could take the product, but 35% said the person should see a doctor or other health professional. This high percentage that needlessly said to consult a health professional suggests that all of the questions in the series may have been influenced by a large conservative bias to not take the medication without consulting a professional. This calls into question the high percentages that answered for the other questions that they should see a doctor.

The results to these questions are in the table below.

Table 5. Correct/acceptable responses to scenario questions

| Symptom :                                                        | Total Correct/Acceptable (%) |
|------------------------------------------------------------------|------------------------------|
| Chest pain, pain spreading to your arms, and shortness of breath | 92                           |
| Frequently wheeze, particularly when you have heartburn (Q.8)    | 94                           |
| Frequent chest pain (Q.9)                                        | 93                           |
| <b>Headache</b>                                                  | <b>100</b>                   |
| Response: OK to take                                             | 66                           |
| Response: See doctor or health professional                      | 35                           |

### Discussion

The study was limited to persons who had certain health conditions that were mentioned on the label as requiring consultation with a physician before using Prilosec 1. There was no attempt in this study to determine if persons taking the medications listed on the label under the section "Ask a doctor or pharmacist before use if you are taking" would understand they should not use the product without a physician or pharmacist consultation.

The study should have excluded persons who now or in the past took Prilosec, as they would have knowledge about the product that goes beyond the label they were shown.

Participants were told that the purpose of the study is to be sure people can understand if they can use the product and how to use it safely and effectively. This information may have unnecessarily guided participants' attention to the important issues of the study before they were asked any questions. The negative effect of this type of statement was somewhat mitigated by the fact it was given after the initial examination of the label, but it should not have been stated at all.

Under the sponsor's analysis, 81% responded correctly when asked if they could use the product. However, we have serious reservations about how respondents were classified for purposes of this question. The most serious concern involves the fact that anyone who had ever discussed his or her contraindicated condition with a health care provider was treated as if that person had received approval to use Prilosec 1. Of course, it is likely most did **not** discuss Prilosec with a health care provider. This classification problem is further compounded by the fact that there is no time limitation on when the problem would have been discussed with a health care provider. It could have been years ago. The results show that 52% had ever reported their symptoms to a health care provider (Question M11). All of these were classified by the sponsor as responding correctly if they said they could use the product. The person who said he or she spoke with a pharmacist was inappropriately scored as acceptable when he or she said the product could be used. Only those who said they would not use the product or who would consult a doctor should have been scored as correct. Those who did not report their contraindicated condition to a health care provider answered the self-selection question correctly only half the time. These participants were not scored as answering correctly or acceptably unless they stated that they would not use the product or would ask a health care provider before use.

Using the sponsor's figures (but not the sponsor's conclusions), a significant proportion of those who should contact a doctor before use stated they could use Prilosec 1, without mentioning the need to see a doctor. In the Agency analysis, more than half (53%) answered this question incorrectly. These results suggest that the tested label did **not** adequately persuade consumers with conditions listed on the label that they must not use the product without consulting a doctor. An Actual Use study would be a useful adjunct to these findings to see how well potential users selected in a more realistic situation.

### Conclusions

These results strongly suggest that persons with conditions listed on the tested label as needing a physician's advice may not be inclined to consult a physician. The sponsor's categorization of persons who ever consulted a health care provider (or pharmacist) for their contraindicated condition as being appropriate to use the product is a leap of faith. Seeing the health care professional for the condition is not a surrogate for asking if one can use Prilosec 1 if one has the condition. Speaking with a pharmacist is also not a substitute for talking with a physician about using Prilosec 1. Of particular concern is the fact that half of those who did not discuss their medical condition with a health care provider did not state they should consult one before using the product.

Participants showed a 100% level of understanding that the purpose of the product is for heartburn; about 80% understood it is for frequent heartburn, but relatively few (40%) mentioned prevention.

The scenario questions indicate a fairly good understanding of the advice on the label that says to ask the doctor if one has chest pain or wheezing. However, the high proportion of

responses to the headache question that one should consult a doctor suggests that responses to these questions may be driven by an unusual conservative bias that may be an artifact of the study and may not exist in actual use.

We do not have a good explanation for why answers to scenario questions are correct at a higher rate than responses to the self-selection question. This disconnect suggests participants may understand the contraindicated conditions on the label but have trouble applying the warnings to themselves. Alternatively, it is possible that, despite the care taken in crafting the self-selection questions, participants still did not understand the purpose of the question. This inconsistency merits close scrutiny in the actual use study to see if, in a more realistic situation, persons with the listed conditions would see a doctor before use or would decline to use the product.

The label was not changed after this study to improve the presentation of conditions requiring physician consultation or to emphasize that the product is for prevention.

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MEDICAL OFFICER

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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Date: May 17, 2002

From: OTC Omeprazole Magnesium (Prilosec 1™) Review Team

To: Gastrointestinal and Nonprescription Drug Advisory Committee Members, Consultants and Guests

Through: Division of Gastrointestinal and Coagulation Drug Products  
Division of Over-the-Counter Drug Products

Subject: NDA: 21-229: Prilosec 1 (omeprazole magnesium) for OTC Use

**Background**

Omeprazole, a proton-pump inhibitor, was approved for prescription use in 1989 and is currently marketed for the following indications:

- For the treatment of duodenal and gastric ulcer;
- For the treatment of gastroesophageal reflux disease (GERD);
- For the maintenance of healing of erosive gastritis;
- For the long-term treatment of pathological hypersecretory conditions.

The recommended dose and treatment duration range from 20 mg daily for up to 4 weeks for short-term symptomatic GERD to 20 mg daily for up to 12 months (for maintenance of healing of erosive esophagitis).

Currently there are two classes of drug products available OTC for use in heartburn: antacids and acid reducers also known as histamine-2 receptor antagonists (H2AR). Both of these classes of drugs are indicated for the treatment of acute occasional heartburn symptoms. The acid reducers have the additional claim for the prevention of meal-induced heartburn at specified times depending upon the product. The 24-hour prevention claim is one not currently available in the OTC market.

The switch of Prilosec from Rx to OTC was previously discussed on October 20, 2000 at a joint advisory committee composed of individuals from the two committees represented today. Originally, the sponsor sought to market Prilosec 1 OTC for the same indications for which OTC antacids and OTC H2-receptor antagonists are approved: "relief of heartburn, acid indigestion and sour stomach; and prevention of these symptoms brought on by consuming certain foods and beverages; and the prevention of symptoms for 24 hours." During that meeting efficacy, safety, pharmacokinetic issues, and consumers' ability to understand and use the product correctly without a learned intermediary were discussed. The Committees felt that adequate data had not been presented to support these indications for Prilosec OTC and approval was not recommended. However, the Committee indicated that the safety profile was such that Prilosec could be switched OTC if a suitable population could be identified that could use this product safely and effectively.

Based on the committee opinion, as well as subsequent discussions with the Agency, the sponsor submitted their completed response to the Agency in February 2002. In that response, the sponsor stated that the target OTC population are those suffering from "frequent heartburn. As such they modified the indication to: "for the prevention of frequent heartburn," "intended for those who suffer heartburn two or more days a week." In addition, they proposed modified versions of the directions for use. In support of these modifications, the sponsor submitted data obtained from an actual use and two label comprehension trials to address appropriate selection/deselection, expectation of benefits, and how this product would fit into the armamentarium of OTC "heartburn" therapy. In addition, to support the proposed 20.6 mg omeprazole magnesium dose, the sponsor relied on pharmacodynamic data showing more consistent acid

suppression at 20 mg than at 10 mg and that 20 mg provided a directionally higher level of prevention across all temporal variables than 10 mg, which was the dose previously proposed for OTC use. This data was discussed at the advisory committee meeting in October 2000. Further, the proposed 14-day duration of consecutive daily doses is proposed based on the efficacy data from the OTC trials and from the Actual Use trials.

#### **FDA Reviews**

##### *24-h Prevention: Results of Studies 171 and 183*

These studies were randomized, double blind, multicenter, placebo-controlled trials to assess the efficacy of Prilosec 10mg and 20mg OTC in the prevention of further heartburn episodes. Entry criteria consisted of having heartburn of greater than 1-month duration, with a frequency of at least 2 heartburn episodes per week. An antacid or OTC H2RA responsive population was recruited. The results of the primary efficacy variable, the proportion of subjects with no heartburn over 24h, and at 14 days (secondary variable) are as follows:

- A substantial proportion of subjects experienced no heartburn on Day 1 or Day 14 in the placebo group.
- The therapeutic gain with Prilosec, although statistically significant, is only modest on Day 1.
- The therapeutic gain increases on Day 14, confirming that the maximum benefit of treatment relies on consecutive dosing.
- Approximately 30% of participants experience "breakthrough" heartburn on Day 14. This is defined as having an episode of heartburn despite using the medication according to directions.
- The proportion of responders is higher in subjects with low frequency heartburn at baseline versus high frequency; although the therapeutic gain is small.
- There is approximately a 40% treatment failure rate after 14 Days in subjects with high frequency heartburn at baseline, with the benefit being lost within 3 days of discontinuation of therapy.

#### *Biopharm Issues*

The pharmacokinetic profile of Prilosec is useful in understanding its efficacy. The half-life of omeprazole is short, 0.5-1 hour. There is also a slow pharmacodynamic onset, with acid inhibition only 50% of maximum at 24 hours, and a long-acting pharmacodynamic effect of acid secretion reduction to baseline over 3-5 days. It is these effects that make Prilosec ineffective in acute relief and make it beneficial for 24-hour prevention.

With regard to drug-drug interactions, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, R-warfarin, and tolbutamide. These effects may be clinically significant in susceptible individuals, such as those having liver disease. Thus, caution, in general, needs to be exercised when co-administering the above drugs with omeprazole.

#### *Safety*

The frequency of adverse events (AE) reported in the clinical trials were similar to those known for the prescription products, with regard to headaches (5%), infection (2%), and diarrhea (2%), without dose-related differences. The frequency of AEs reported in the Actual Use study was similar: headache (17.9%), diarrhea (3.8%), and abdominal pain (3.2%). Most of these reactions were not dose-dependent, and were transient in nature. The Safety Update did not reveal any new safety areas of concern.

#### *Actual Use Trial (#007)*

This was a multi-site, multi-dose, open-label, observational study of OTC consumers ("all-comers"), conducted in 5 different cities in the United States. Potential subjects were recruited from a variety of advertising media. The objectives of this study were to determine:

- The percentage of subjects who correctly self-selected that the study medication was a drug that they could or could not use;
- The percentage of doses where no more than one tablet of study medication was taken per dose;
- The percentage of dosing days where no more than one dose and no more than one tablet of study medication was taken per day;
- The percentage of subjects who took between 11-14 doses of study medication in an 11-17 day period (80-120% of dosing directions).

A total of 1301 consumers participated in the self-selection portion of the study. Of those, 1251 (96%) stated that Prilosec 1 was appropriate for them to use and 863 agreed to participate in the study. Of these, 854 purchased the study medication; 782 completed the study; and 758 actually purchased and used the drug. Overall, 83% of the primary population (those treating themselves with the drug) and 76% of the secondary population (those making a determination that the drug was appropriate to use) correctly self-selected. (Of note, the primary population is composed of people who had gone through 2 screening processes; whereas, the secondary population had undergone only one screening process.) Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. In addition, 13.5% of the self-selection (secondary) and 9% of the treated (primary) population who had infrequent heartburn ( $\leq 1$  day a week) and 8.2% has contraindicated conditions, classifying them as inappropriately self-selecting. Overall, compliance with the three-labeled directions (take 1 tablet a day, every day for 14 days) was achieved by 63% of the treated population. Compliance increased to 79% if the sponsor analyzed compliance as subjects taking between 11 to 14 doses of study medication in an 11-17 day period. Three percent exceeded 14 consecutive days of treatment and 33% took the drug for less than 14 days. The study showed that the majority of those using Prilosec 1 have long-standing heartburn. However, only 48% of those had spoken to their physician within the last year, and 35% had not spoken to a health care provider at all. The responses to the follow-up questionnaire (3 months after the study) showed that 58% of the consumers available for follow-up had their heartburn return; 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

#### *Pregnancy Category*

Pregnancy Category C is the recommended designation; based on the effects on the human fetus, especially developmental and behavioral, which have not been adequately defined. Based on the mechanism of action of the drug and the consistent results amongst several animal species, exposure to pregnant women should be limited.

#### *Labeling Comprehension*

Two label comprehension trials were undertaken to address the issue of whether consumers could understand the distinction between Prilosec 1 and the currently marketed antacids and H2RA. Of note, the label used in both studies was not the same one used in the Actual Use Study, as these studies were conducted simultaneously. However, the label used in the Actual Use trial was similar to those being tested in the label comprehension trials.

Study 2255 suggests that the tested label does not adequately convey to consumers that the product is not for episodic use and that it is only for prevention. Further, the study also indicates that many who may choose to take this product are also using contraindicated medications or have contraindicated conditions, and may not check with a health care provider prior to taking Prilosec 1.

Study 12179 was conducted among persons who should consult a physician before using Prilosec 1 due to medical conditions. The results suggest that most people who should consult a physician before using the product may not understand that they should do so. Among participants, there was a good understanding of the use for frequent heartburn, but a low demonstration of understanding that the use is limited to prevention. After the study, the label was not substantially changed to improve the understanding in these areas.

## Discussion

There are some very specific issues that need to be addressed in considering the safe and effective use of Prilosec 1 in the OTC setting. Despite a relatively short half-life of 2 hours, the pharmacodynamic effect can be measured for 3-5 days after initial administration. The mechanism of action, which has been described as an irreversible inhibition of the proton pump, has a half-life of 50 hours. These characteristics make the product less effective for relieving acute heartburn pain. However, the prolonged pump inhibition that makes this a successful product for repeated (chronic) administration, which is consistent with the new indication sought.

In light of the pharmacological characteristics, one of the questions to be addressed was whether consumers will accurately self-select for (or against) the prevention of frequent heartburn occurring two or more times per week. Overall, the Actual Use study showed that 76% correctly self-selected that the product was appropriate for them to use. This percentage is based on initial self-selection after picking up the product and reading the label. The percentage of correctly self-selecting is higher (83%) if the population that actually self-selected to participate and use the product is used. The majority of those enrolled (87%) and the majority of those treated (91%) had frequent heartburn as defined by having  $\geq 2$  episodes per week. Thus, the self-selection rate was better in those who actually chose to use the product.

The data from the Actual Use study also showed that the majority (98%) of those using Prilosec 1 had heartburn symptoms for more than 3 months; 48% of those had spoken with their physician or health care provider within the past year; and 35% had not spoken to a health care provider about their heartburn ever. This raises an issue that, if available OTC, consumers might not appropriately follow-up with a health care practitioner to identify and treat their underlying condition and may, simply choose to continue treatment if symptomatic relief is afforded.

As studied in the Actual Use trial, the duration of treatment for OTC use was 14 days of continuous use. The majority (97%) of the treated population did not exceed 14 consecutive days of therapy. Overall compliance with all three labeled directions: one tablet a day, every day, for 14 days, was achieved by 63% of the treated population. The difference in the percentages are due to the fact that: not all consumers took only one tablet of Prilosec 1 per dose, not all used just one tablet a day; or not all took medication continuously for 14 days. The responses to the 3-month follow-up questionnaire showed that 58% of the available participants had their heartburn return. Of these, 46% took an antacid heartburn medication; 27% took a prescription heartburn medication; 21% took an OTC acid reducer; 20% of those contacted their health care provider; 10% changed life-style; 8% did something else (not specified); and 6% did nothing.

The label comprehension trials showed that approximately 80% of the participants understood that Prilosec 1 was for frequent heartburn. It was unclear from these studies, due to the way the questions were worded, if consumers understood that Prilosec 1 was intended for prevention only and not for acute or episodic relief.

An additional issue to be addressed is the consequences of long-term and/or chronic intermittent treatment without physician oversight and whether any of the more significant conditions may be masked as a result of consumers choosing to continue to medicate rather than follow-up with a health care provider. Given the targeted population for use (those with frequent heartburn), the issue remains as to whether the proposed duration of therapy (14 continuous days) should be influenced by the likelihood that patients with GERD (having a minimum duration of prescription therapy of 4 weeks) might purchase the medicine.

In summary, when reviewing the data presented in the briefing package consideration should be given to the following issues:

- Has the sponsor identified an acceptable target population?
- What is the appropriate duration of therapy ?
- How should acute and episodic, as well as long-term intermittent use be addressed?

**Review**  
**Division of Surveillance, Research, and Communication Support**

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>NDA #</b>                      | 21-229                              |
| <b>Drug:</b>                      | Omeprazole Magnesium Tablets        |
| <b>Sponsor:</b>                   | The Procter & Gamble Co.            |
| <b>Identification:</b>            | Study 02255 Label Comprehension     |
| <b>Date of Reviewed Document:</b> | July 20, 2001                       |
| <b>Reviewer:</b>                  | Karen Lechter, J.D., Ph.D., HFD-410 |
| <b>Review Completed:</b>          | May 6, 2002                         |

**Overview**

The results of this label comprehension study strongly suggest that the tested label does not adequately convey to consumers the product is not for episodic use and that it is only for prevention. Further, it is likely that many who take contraindicated medications and many with contraindicated conditions will believe they can take Prilosec 1 without checking with a health professional. Some of the high levels of correct responses may have been due to an artifact of the questioning by which almost all questions required responses that the product should not be used or a health professional should be consulted.

**Communication Objectives**

The following are the key communication objectives of the study:

- 1) Consumers understand the uses of the product
  - a) Prilosec 1 is for prevention of frequent heartburn.
  - b) Prilosec 1 is only for those who suffer heartburn two or more days a week.
- 2) Consumers understand who can and cannot use Prilosec 1 (warnings).
  - a) Do not use if you are allergic to omeprazole.
  - b) Notify your doctor if you have had heartburn for three months or longer and have not talked to your doctor about it.
  - c) Do not use if you have trouble swallowing food, wheezing, a chronic cough or hoarseness, have vomited blood, black/tarry stools, chest pain, or unexplained weight loss.
  - d) Do not use if you have a sudden increase of your heartburn symptoms with nausea and vomiting; chest pain; pain spreading to your arms, neck or shoulders; sweating; shortness of breath or lightheadedness.
  - e) Do not use with other acid reducers.
- 3) Consumers understand under what conditions one must first ask their doctor or pharmacist before using Prilosec 1 (warnings).
  - a) Ask a doctor or pharmacist before use if you are taking warfarin, phenytoin, diazepam, clarithromycin, itraconazole and/or ketoconazole.
  - b) If pregnant or breast-feeding, ask a health professional before use.
  - c) Children under 18 years of age: ask a doctor.
- 4) Consumers understand the condition under which Prilosec 1 can and cannot be used (warnings).

- a) Stop use and ask a doctor if stomach pain continues or worsens.
  - b) Stop use and ask a doctor if heartburn continues or returns after using this product everyday for 14 days.
- 5) Consumers understand how to use Prilosec 1 safely and effectively (directions).
- a) For prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning.
  - b) Take every day for 14 days.
  - c) Do not continue beyond 14 days unless directed by your doctor.
  - d) Do not take more than 1 tablet a day.

## **Methodology**

### **Participants**

There were five cohorts of adult males and females, 18 years of age and older.

- 1) General population adults (n=297)
- 2) High literate frequent heartburn sufferers (n=155)
  - above 8<sup>th</sup> grade reading level
  - experience heartburn 2 or more days a week or currently take prescription heartburn medication
- 3) Low literate frequent heartburn sufferers (n=162)
  - 8<sup>th</sup> grade reading level or lower
  - experience heartburn 2 or more days a week or currently take prescription heartburn medication
- 4) Drug interaction heartburn sufferers (n=96)
  - currently experience heartburn, have experienced it in the past 6 months, or currently take prescription heartburn medication
  - currently take warfarin, phenytoin, diazepam, clarithromycin, itraconazole, and/or ketoconazole
  - have no condition listed on the label that would prevent them from using the product or that would require them to consult a doctor or pharmacist before use, other than the drug interaction
- 5) Pregnant/Nursing heartburn sufferers (n=42)
  - currently experience heartburn, have experienced it in the past 6 months, or currently take prescription heartburn medication
  - pregnant or nursing
  - have no condition listed on the label that would prevent them from using the product or that would require them to consult a doctor or pharmacist before use, other than pregnancy or nursing

### **Procedure**

Most participants were recruited in ten geographically dispersed shopping malls around the country. Participants recruited in malls were screened for qualifications. Those who qualified were taken to a facility in the mall and were interviewed. The majority of the drug interaction heartburn sufferers (Cohort 4) were recruited using advertising, screened by telephone, and asked to come to a central location for the interview. The pregnant and

nursing heartburn sufferers (Cohort 5) were recruited primarily by telephone using agency databases, and were asked to come to a central location for the interview.

All who qualified were given the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy test. They then examined the label before they were asked questions about it. Non-sufferers were not asked all the questions. They were asked only about the purpose of the product, whether they could use it themselves, and they provided demographic and medical information relevant to product use. Pregnant or nursing participants were asked only about product use, whether they could use it themselves, and questions about use by pregnant and nursing women. They also provided demographic and medical information relevant to using the product. All others answered the full questionnaire. All had the label available to examine during questioning.

There were two different versions of the full questionnaire. Half of the drug interaction scenarios and half of the heartburn warning symptom questions were presented in each version to reduce the length of the questionnaire.

#### Recruitment Advertisement and Screening Questionnaire

*Comments.* An advertisement was used to recruit Cohort 4, the heartburn sufferers who are currently taking prescription medications listed on the label as requiring physician input. This advertisement listed only those classes of medications listed in the label. It is possible that the information in the advertisement, by not including other "false" medication classes, may have alerted consumers to the possibility that certain types of medications were important to the study. This may have biased the results by making participants' medications more salient to them as factors in the study, making it more likely they would answer questions about their own use of the product correctly. It would have been better to use a longer list of drug classes or to make a more general statement about taking any prescription medicines, or to say nothing about medicines. If nothing was on the advertisement about medicines, along with other questions, callers could have been asked if they took any medicines, to divert them from the true purpose of the questioning. This would not have given them specific clues about what the study was interested in, as the actual advertisement did.

#### Main Questionnaire

*Comments.* In the series of scenario questions (beginning with Q.2) about use for episodic heartburn, five questions should be answered "no" and only two "yes." It would have been better to have a more even balance so participants would not develop a nay-saying bias based on the pattern of questions. At some point, participants might realize that most questions should be answered "no." This feature of the questioning may be a possible source of bias. It is good practice to have more balance in such a series.

Q. 13 was asked only of the drug interaction cohort (Cohort 4). If, in response to the self-selection question (Q. 11), these participants answered incorrectly that they could use the product, they were asked Q. 13 in which they were provided with a list of contraindicated

drugs with their brand and generic names to help them respond. This question is troublesome for two reasons. First, consumers in retail settings would not be given a card with the contraindicated medications on it before examining the label. Second, both the generic and brand names are provided. In normal use, consumers would have to depend on their knowledge of their own medications to determine if they take a contraindicated medication. They would not have a reference list giving them the generic names for contraindicated products they might take. The results of Q. 13 are therefore of dubious value.

When scenario questions were answered incorrectly, participants were asked to give a reason for their response. It would have been better to ask the basis for all responses for two reasons. First, participants' reasons for giving the correct response may not be based on the label, and second, participants may notice that they are not always asked why they responded as they did. They may correctly conclude that the quality of their responses drives the interviewer's decision to ask for a reason, and this may provide them feedback that would affect the questioning process.

A series of 11 questions in a row (Q.15-Q.35) contains only one that should be answered affirmatively and ten that should not. This may have established a nay-saying bias that would make it more likely that responses would be correct. Correct responses may therefore be artificially inflated.

In the next series, a group of seven questions (Q.42-Q.50), all require that the person see a doctor or not use the product. A nay-saying bias could have affected these results, providing for more correct responses than would be the case if there were more balanced responses required.

## **Results and Discussion**

Open-ended questions were scored as correct, acceptable, or incorrect. Correct responses were those that were correct initially or in a follow-up probe. Responses were acceptable if they did not reflect information on the label, but would not be incorrect product usage, such as asking a doctor when it is not necessary.

**Product Purpose.** In general, participants did not give full responses to the question about the purpose for product use. They either left out the idea of prevention or the idea of the necessity for frequent heartburn. When asked what the product is to be used for, only 39% of the general population responded with "prevent frequent heartburn. The literate frequent sufferers answered this question correctly 39% of the time, and the low literate frequent sufferers 36% of the time. Almost everyone else gave a partial response, even after probing, with answers such as "heartburn," "prevent heartburn," and "frequent heartburn."

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Table 1. Responses to question about purpose of product.

| Purpose                          | General Population (%) n=297 | Literate Frequent Sufferers (%) n=155 | Low Literate Frequent Sufferers (%) n=162 |
|----------------------------------|------------------------------|---------------------------------------|-------------------------------------------|
| Complete:<br>Prevent frequent HB | 39                           | 39                                    | 36                                        |
| Incomplete:<br>Heartburn         | 40                           | 45*                                   | 24                                        |
| Prevent HB                       | 6                            | 4                                     | 20*                                       |
| Frequent or 2+ days/week HB      | 13                           | 10                                    | 18                                        |
| Acid reflux                      | 2                            | 2                                     | 2                                         |

\*statistically significant difference between literacy groups at 95% confidence level

Questions about use for relief or prevention of heartburn episodes resulted in low proportions of correct responses. Approximately half of the general population believed the product was appropriate for relief and prevention of individual heartburn episodes. For three of the five questions in this area, the frequent sufferers, low and higher literacy, responded in the low to mid-sixty percent. Responses to this question indicate the label did not communicate the prevention message adequately. If there were no nay-saying response bias for this series of questions (discussed earlier), scores may have been even lower. These were all questions for which a correct response was that the product should not be used. Many participants seemed not to understand not to use the product episodically or for relief.

Table 2. Correct responses to episodic heartburn questions.

| Q. | Episodic                 | General Population (%) n=297 | Literate Freq. Sufferers (%) n=155 | Low Literate Freq. Sufferers (%) n=162 |
|----|--------------------------|------------------------------|------------------------------------|----------------------------------------|
| 2  | relief                   | 55                           | 61*                                | 49                                     |
| 3  | relief                   | 52                           | 67                                 | 66                                     |
| 5  | relief in freq. sufferer | 48                           | 51                                 | 59                                     |
| 6  | prevent                  | 54                           | 57                                 | 63                                     |
| 8  | prevent                  | 61                           | 65                                 | 65                                     |

\*statistically significant difference between literacy groups at 95% confidence level

For two questions about using the product to prevent frequent heartburn, responses were generally above 80-90%. These were the two questions for which the correct response was that it was appropriate to use the product.

Table 3. Correct responses to frequent heartburn questions.

| Q. | Frequent | General Population (%)<br>n=297 | Literate Freq. Sufferers (%)<br>n=155 | Low Literate Freq. Sufferers (%)<br>n=162 |
|----|----------|---------------------------------|---------------------------------------|-------------------------------------------|
| 4  | prevent  | 93                              | 94*                                   | 79                                        |
| 7  | prevent  | 83                              | 87                                    | 83                                        |

\*statistically significant difference between literacy groups at 95% confidence level

**Self-selection.** When asked if they, themselves, could use the product, the range of correct responses in the group that should not use the product or should consult a physician varied from 41% to 91%. Of the total, 67% were correct overall. For one group, frequent heartburn sufferers with contraindicated medication, scores rose from 50% to 86% after seeing a list of the brand names of the drugs they use. However, in a purchase situation, these types of consumers would be unlikely to have access to a list of the brand and corresponding generic names. Thus, the 50% score is probably more representative of the types of decisions they would be likely to make based on the label. The highest scoring group was those who were allergic. There were only seven members of this group, so the results may not be representative. It is important to note that those who have contraindicated symptoms or who took contraindicated medication selected for themselves incorrectly at least 50% of the time.

Table 4. Responses to self-selection questions for those who should not use (Q9-14)

| Participant Characteristics                                       | Correct/Acceptable (%) | Incorrect (%) |
|-------------------------------------------------------------------|------------------------|---------------|
| Total (n=459)                                                     | 67                     | 33            |
| Non HB sufferer (n=137)                                           | 80                     | 20            |
| Infrequent HB sufferer<br>n=92                                    | 76                     | 24            |
| Frequent HB sufferer<br>allergic to omeprazole(n=7)               | 86                     | 14            |
| Frequent HB sufferer with<br>contraindicated symptom<br>(n=85)    | 41                     | 59            |
| Frequent HB sufferer with<br>contraindicated medication<br>(n=96) | 50                     | 50            |
| After see brand names                                             | 82                     | 18            |
| HB sufferers and pregnant<br>or nursing (n=42)                    | 91                     | 10            |

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**Use with health conditions.** Responses to scenario questions about whether individuals with particular health conditions could take the product were generally good, ranging

from 89%-91% in the general population, and from 90% to 100% in the two literacy groups. However, these questions were in a series that could have established a nay-saying bias, as mentioned earlier. These high scores may have been due, in part, to participants' realizing that almost every response should be not to use the product or to see a doctor.

**Table 5. Correct/acceptable responses to scenarios about taking product with different conditions**

| Q.    | Condition                                                             | General Pop (%)<br>(base n) | Literate Freq. Sufferers (%)<br>(base n) | Low Literate Freq. Sufferers (%)<br>(base n) |
|-------|-----------------------------------------------------------------------|-----------------------------|------------------------------------------|----------------------------------------------|
| 15    | Allergic                                                              | 91 (158)                    | 92 (155)                                 | 94 (162)                                     |
| 17    | Heartburn 6 months; no doctor                                         | 89 (160)                    | 95 (155)                                 | 95 (162)                                     |
| 18/19 | trouble swallowing                                                    | 89 (83)                     | 90 (79)                                  | 95 (109)                                     |
| 20/21 | chest pain, pain spreading to arms and shoulders, shortness of breath | 94 (83)                     | 96 (79)                                  | 95 (109)                                     |
| 22/23 | chronic cough                                                         | 89 (75)                     | 93 (76)                                  | 94 (53)                                      |
| 24    | black tarry stools                                                    | 98 (83)                     | 99 (79)                                  | 99 (109)                                     |
| 25    | unexplained weight loss                                               | 96 (75)                     | 97 (76)                                  | 100 (53)                                     |
| 27    | heartburn worse; nausea, vomiting                                     | 98 (158)                    | 98 (155)                                 | 96 (162)                                     |

There were very high percentages of correct responses to questions about use by pregnant and nursing women and by children. Again, these questions were in a nay-saying series.

**Table 6. Use with pregnancy, nursing, children**

| Q. | condition/status | General Pop (%)<br>(base n) | Literate Freq. Sufferers (%)<br>(base n) | Low Literate Freq. Sufferers (%)<br>(base n) |
|----|------------------|-----------------------------|------------------------------------------|----------------------------------------------|
| 48 | breast-feeding   | 99 (90)                     | 100 (81)                                 | 98 (86)                                      |
| 49 | pregnant         | 98 (90)                     | 100 (81)                                 | 99 (86)                                      |
| 50 | age 15           | 96 (158)                    | 99 (155)                                 | 96 (162)                                     |

**Use with other products.** Correct responses to questions about use with other products were generally very high, ranging from 91-100%. for some of these products, consumers should consult a physician or pharmacist before using Prilosec 1.

**Table 7. Use with other products**

| Q.    | Product                   | General Population (%)<br>(base n) | Literate Freq. Sufferers (%)<br>(base n) | Low Literate Freq. Sufferers (%)<br>(base n) |
|-------|---------------------------|------------------------------------|------------------------------------------|----------------------------------------------|
| 28/29 | other acid reducers       | 91 (158)                           | 89 (155)                                 | 97* (162)                                    |
| 30    | warfarin                  | 98 (83)                            | 99 (79)                                  | 98 (98)                                      |
| 31    | phenytoin                 | 100 (75)                           | 100 (76)                                 | 98 (53)                                      |
| 34    | diazepam                  | 98 (83)                            | 98 (79)                                  | 99 (109)                                     |
| 37    | antibiotic clarithromycin | 99 (75)                            | 97 (76)                                  | 98 (53)                                      |
| 42    | itraconazole              | 98 (42)                            | 99 (79)                                  | 98 (109)                                     |
| 43    | ketoconazole              | 97 (75)                            | 100 (76)                                 | 100 (53)                                     |
| 35/36 | Tylenol                   | 93 (158)                           | 97 (155)                                 | 93 (162)                                     |

\*statistically significant difference between literacy groups at 95% confidence level

There seemed to be very good scores for what actions to take while using the product, including when to stop taking it, how long to use it, and when and how much to dose. However, some of these questions (33, 44, 46, 47) were in a nay-saying series.

**Table 8. Actions During Use**

| Q. | Situation                             | General Pop Correct/ Acceptable (%)<br>(base n) | Literate Freq. Sufferers Correct/Acceptable (%)<br>(base n) | Low Literate Freq. Sufferers Correct/Acceptable (%)<br>(base n) |
|----|---------------------------------------|-------------------------------------------------|-------------------------------------------------------------|-----------------------------------------------------------------|
| 44 | stomach pain worse                    | 100 (158)                                       | 100 (155)                                                   | 100 (162)                                                       |
| 47 | more than 14 days                     | 96 (158)                                        | 96 (155)                                                    | 96 (162)                                                        |
| 33 | more than 14 days                     | 89 (158)                                        | 94 (155)                                                    | 93 (162)                                                        |
| 38 | time to take dose                     | 85 (158)                                        | 88 (155)                                                    | 83 (162)                                                        |
| 39 | # tablets daily                       | 98 (158)                                        | 99* (155)                                                   | 89 (162)                                                        |
| 46 | take an extra for episodic prevention | 97 (158)                                        | 98 (155)                                                    | 94 (162)                                                        |
| 40 | dosing frequency                      | 98 (158)                                        | 98 (155)                                                    | 88 (162)                                                        |
| 41 | how long take                         | 94 (158)                                        | 95* (155)                                                   | 82 (162)                                                        |

\*statistically significant difference between literacy groups at 95% confidence level

Because this questionnaire overwhelmingly contained questions that required responses that the product should not be used or that a doctor or pharmacist should be consulted, a strong nay-saying bias may have been responsible for the very high scores in these series. Thus, the scores are of questionable reliability and validity. It would have been much better to have more questions that did not preclude taking the medication or taking the other action that was mentioned in some of the questions.

### **Conclusion and comparison of tested label with proposed label**

These results suggest that the tested label does not adequately convey to consumers the following:

- the product is not for episodic use and
- the product is only for prevention

Based on results of the self-selection question, it is not clear consumers will understand that the product should not be used with certain other medications or with certain health conditions unless one checks with a doctor or pharmacist.

Some of the high levels of correct responses to the scenario questions may have been due to an artifact of the questioning by which almost all questions required responses that the product should not be used or a health professional should be consulted.

If one compares the tested label with the proposed label for these areas of sub-optimal communication, one finds that there has been little or no change to the label to improve communication of some of these messages. In the proposed label, the prevention message is the same, with added wording about preventing symptoms and 24 hour coverage. The tested label says "for prevention of frequent heartburn." The proposed label says "for prevention of the symptoms of frequent heartburn for 24 hours." There is nothing on either label to indicate that episodic use is inappropriate, other than the directions to use it every day for 14 days. This message is the same on the tested and proposed labels.

The proposed label lists only three products that require consultation with a health professional, while the tested label had six. The section in the tested label that said "Do not use" contained lists of multiple conditions under two bullets that require the person consult a physician. In the proposed label, these are broken into five bullets, which may be easier to read and to process cognitively.

The "do not use" section of the tested label has been changed to "Ask a doctor before use if you have" in the proposed label. Furthermore, some conditions in the tested label are not in the proposed label. These include chronic cough or hoarseness, vomiting blood, black tarry stools, and sudden increase in symptoms with nausea and vomiting. The proposed label has five bullets in this section, while the tested label had only three covering more conditions. The resultant label section in the proposed label is shorter and easier to read and process. However, it has not strengthened the message about prevention or that it is not for episodic use. It is improved regarding use with other

medicines because that section is shorter. It is improved regarding use with certain medical conditions because that section is shorter and has more bullets.

Testing of the proposed label is necessary to conclude whether it communicates better than the tested label in critical areas.

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MEDICAL OFFICER

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NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: Douglas Ws. Bierer, Ph.D.  
Director, Regulatory Affairs  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

2-MAY-2002

Dear Dr. Bierer:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We also refer to your submission dated April 9, 2002, which included an overview of your briefing document for the upcoming meeting of the Joint Advisory Committee and your request for the Agency's comments.

We have reviewed your submission and have the following comments.

In addition to the topics you have identified, you should also address the following issues:

1. In the Efficacy section (4.0), a summary of data from Studies 171 and 183 that demonstrates the increases in therapeutic margins of Prilosec 1 vs. placebo over the entire 14-day treatment period should be presented. Attention to the buildup of therapeutic gains during consecutive daily treatment (Prilosec vs. placebo) (e.g., the percentage of subjects with no heartburn over 24 hours on Day 14 vs. Day 1 of treatment, as well as other treatment Days vs. Day 1) and dose responses (10 mg vs. 20 mg) should be drawn.
2. In the Dose and Duration section (6.0), a discussion of the clinical condition of Study Subjects and Targeted Consumers should be provided. In particular, implications of the observation made by panelists and a number of expert lecturers at the October 20, 2000 Joint Advisory Committee meeting that a significant number of subjects with gastroesophageal reflux disease (GERD) will be treated should be analyzed. These include:
  - a) Reconciling the proposed 14-day OTC treatment plan with the management of GERD in a doctor's office setting [proton pump inhibitor (PPI) treatment doses and treatment duration].

- b) Reconciling the high relapse rates and rapid speed of relapse of GERD symptoms after cessation of PPI treatment (as studied in the literature) with the OTC treatment plan of a single 14-day treatment course.
3. In the Appropriateness of OTC Use section (8.0), include the following items:
- a) A discussion of the management of intermittent flares of heartburn over a long-term period. For example, if there are 3 flares per year, do you intend that the consumer will self-medicate over 3 separate 14-day treatment courses?
  - b) The acceptable limits of the frequency of intermittent treatments from a safety perspective.
  - c) An analysis about the likely pattern of actual Prilosec 1 usage in an OTC setting over a long-term period.

If you have any questions, call Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Victor F.C. Raczowski, M.D., M.S.  
Acting Director  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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## MEMORANDUM OF TELECON

DATE: April 29, 2002

APPLICATION NUMBER: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Linda Jones, Regulatory Affairs  
Phone: (513) 622-3176  
Representing: Proctor and Gamble Co.

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Information Request re: Label Comprehension Study 12179

BACKGROUND: The sponsor submitted a complete response to the November 27, 2000 action letter on February 12, 2002. Karen Lechter is reviewing Label Comprehension Study 12179 and asked me to convey the following information requests to the sponsor.

1. Please clarify the number of people who were classified as having infrequent symptoms (Table 1 says 32 and Table 3 says 39).
2. Page 16 (at the top) states that 78% of the subjects understand the product is for prevention of frequent heartburn. The Agency arrives at a number of 57%. Please address this discrepancy.
3. Regarding the results for Question No. 4, please explain why nine of the subjects who said it was OK to use the product classified as "correct."
4. Regarding the results for Question No. 4, please specify who the 19 participants are. Where do they appear in the results for Question No. 2?

TODAY'S CALL: I called Ms. Jones and relayed to her the above information requests for Label Comprehension Study 12179. Ms. Jones said the sponsor would submit a written response as soon as possible. The call was then concluded.

/s/

---

Maria R. Walsh, M.S.  
Regulatory Project Manager

MAY 3 2002

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

DATE:            April 23, 2002

FROM:            Hugo E. Gallo-Torres, M.D., Ph.D.  
                         Medical Team Leader  
                         Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT:        NDA 21-229 [Procter and Gamble (P&G)]  
                         Prilosec 1 (Omeprazole Magnesium Tablets) Resubmission  
                         Re: Briefing Document for June 21, 2002 Advisory Committee Meeting

TO:              Acting Director, Division of Gastrointestinal and Coagulation Drug  
                         Products, HFD-180  
                         Director, HFD-560  
                         Deputy Director, HFD-560

**Prilosec 1 (Omeprazole Magnesium Tables)  
June 21, 2002 Advisory Committee Meeting**

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## I. Background/Introduction

Prilosec (omeprazole =OME) Delayed-Release capsules is a prescription drug product approved for several indications in which effective treatment depends on inhibition of gastric acid secretion. These include the three indications related to gastroesophageal reflux disease (GERD):

- a) short-term treatment of symptomatic GERD (s-GERD);
- b) short-term treatment of erosive esophagitis (EE); and
- c) the maintenance of healing of erosive esophagitis (up to 1 year).

The recommended dose and length of treatment for the three indications are: 20 mg daily for up to 4 weeks for the treatment of s-GERD; 20 mg daily for to 8 weeks for the treatment of patients with EE and accompanying symptoms due to GERD and 20 mg daily for the maintenance of healing of EE, for up to 12 months<sup>1</sup>.

OME belongs to a class of drugs known as proton pump inhibitors (PPIs)<sup>2</sup>. PPIs are substituted benzimidazoles, which irreversibly inhibit active forms of the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme complex ("proton pump") located on the apical membranes of the parietal cells in the stomach. OME is a pro-drug and a lipid-soluble weak base that, at neutral pH, is devoid of gastric acid inhibitory effect. The proposed over-the-counter (OTC) formulation, PRILOSEC 1 (omeprazole magnesium) tablets (OME-Mg), are comprised of individually enteric coated pellets (i.e. multiple unit pellet system-MUPS) which contain the alkaline magnesium salt of omeprazole. Following its systemic absorption, the pro-drug reaches the parietal cell, and is activated by protonization (ionization) in an acidic milieu and rearranges to form sulphenic acid and sulfenamide. The sulphenamide then reacts covalently with the sulphhydryl group of the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme system to inhibit gastric acid secretion<sup>3</sup>.

### Pharmacokinetic (PK)/Pharmacodynamic (PD):

- a short PK half-life (0.5 to 1h), slow PD onset (acid inhibition of only 50% of maximum at 24h) and long-acting PD (antisecretory) effects.

<sup>1</sup> Other indications for which prescription PRILOSEC is approved are: short-term treatment of active duodenal ulcer, H. Pylori eradication for the reduction of the risk of duodenal ulcer recurrence, short-term treatment of gastric ulcer, and treatment of pathological hypersecretory conditions (Zollinger-Ellison syndrome).

<sup>2</sup> Other commercially available drugs in the class are: lansoprazole (PREVACID), rabeprazole (ACIPHEX), pantoprazole (PROTONIX) and esomeprazole (NEXIUM).

<sup>3</sup> The reactions of the PPI with the enzyme is permanent and new H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme needs to be formed to allow the resumption of gastric acid secretion.

contrast, in Study 006, both 10 and 20mg doses were associated with significantly superior responses, compared to placebo. In this trial, secondary endpoints including overall assessment of medication, maximum severity score, backup medication use, average symptom severity, and reduction of maximum severity score were supportive of the 20mg dose. On the other hand, only the maximum severity score was supportive of the 10-mg dose.

The inconsistent results with OME-Mg in Studies 005 and 006 are to be contrasted with historical data that support efficacy of H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs). Members of this class of acid suppressing agents have been shown to consistently prevent heartburn stimulated by a standard meal.

## II. Advisory Committee of October 20, 2000

The merits of the sponsor's original submission were discussed at the Non-Prescription Drugs/Gastrointestinal Drugs (NPDGIAC) Joint Advisory Committee that was held on October 20, 2000.

The sponsor's (Astra Zeneca/Proctor & Gamble) presentation included an overview by Dr. Donald O. Castell, an expert in the field of PPI and GERD. Dr. Castell summarized the "iceberg concept" that pertains to all clinical disease and encompasses the spectrum of gastroesophageal reflux. The largest group of individuals with this condition consists of those who experience episodic, mild heartburn and treat it effectively with life-style changes, antacids or OTC H<sub>2</sub>RAs, but do not bother to visit a doctor with their complaints. The next largest group is those with a pattern of pain severity and frequency of symptoms for which treatment with PPIs or H<sub>2</sub>RAs is needed. The smallest group, at the tip of the iceberg, consists of those patients with symptoms, complaints and complications which must be treated with long-term PPIs or surgery. These latter two groups are the ones who typically visit doctors. Those with the most severe patterns of heartburn or esophagitis, have frequent episodes of reflux, and longer intervals during which the esophageal pH remains below 4. In addition, they tend to have decreased lower esophageal sphincter (LES) pressures. This group of patients can be considered as having a mechanical disorder of the LES and may require surgical correction for restoration of sphincter competence. It should be emphasized that symptom severity does not always predict severity of esophagitis and may not be a good measure of disease severity, since progression of esophageal mucosa damage is occasionally seen in asymptomatic patients. Moreover, esophagitis may progress even with intensive therapy. In addition, the greater the severity of esophagitis, the lower the healing rates. It is not surprising that larger doses of PPIs are often required to effectively treat higher grades of esophagitis.

As part of the sponsor's presentation, Dr. Castell described a survey of 1,004 individuals, which demonstrated that the distribution of frequencies of heartburn in U.S. adults is as follows: daily sufferers, 11%; weekly sufferers, 13%; monthly sufferers, 18%; the reported heartburn in 58% of the individuals was none. According to these data, 50%

of individuals with heartburn have symptomatic GERD (s-GERD) without esophagitis, 40% have endoscopic features of erosive esophagitis, 10% have epithelial metaplasia and 0.5% patient-year have epithelial dysplasia or cancer. Although heartburn is the typical symptom of GERD, its severity does not correlate with the degree of esophageal injury. It was stressed that GERD usually recurs after cessation of effective treatment.

Dr. Castell concluded that: 1) likely indications for OTC OME are prevention of predictable occasional heartburn and management of occasional heartburn (2 of the 3 indications then sought by the sponsor); 2) the safety of long-term omeprazole has been established; and 3) masking of clinically important disease that requires recognition and care by a physician is unlikely if properly labeled. Dr. Castell concluded his presentation by noting that making OME-Mg available in an OTC setting may bring more heartburn patients to physicians.

Efficacy data were reviewed by L. Goldkind, M.D., of FDA, who concluded that the results of clinical trials are based on the following known PD properties of the drug:

- 1) no efficacy at single dose acute treatment of episodic heartburn (HB);
- 2) marginal, yet-to-be properly-replicated efficacy at 1h prevention; and
- 3) an optimal role with consecutive doses in the management of GERD (a new OTC indication), currently "a physician-diagnosed chronic disease requiring 4 to 8 weeks of therapy".

L. Chin, M.D., of FDA described the results from the Actual Use trials that were submitted. Despite cautionary labeling, a substantial number of patients were found to use this medication for more than 24 days. After a presentation of adverse events related to short-term (up to 12 weeks) and long-term (several months and years) use of the drug, M. Avigan, M.D. emphasized the role of adequate labeling to a) ensure only short-term OTC treatment by consumers and self-referral to physicians when symptoms persist; and b) [ensure that patients] recognize toxic effects of the drug. Although safe prescription use of the drug relies on a "learned intermediary" [such as a physician] (to evaluate patient and recognize and manage drug toxicity), safe OTC use solely relies on labeling. In her review of the Label Comprehension data, K. Lechter, J.D., Ph.D., of FDA concluded that the AZ/PG data suggested a potential for substantial "inappropriate use" by persons who should consult a physician first. In addition, the sponsor had not provided/evaluated the most recent proposed label which differed from the tested label.

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A list of FDA safety concerns that were stated at the first AC Meeting included: masking serious disease, potential for genotoxicity, tumorigenicity, and fetal developmental toxicity, rebound hypergastrinemia, drug-drug interactions and discussions on the actual use and label comprehension issues.

At the time of the first Advisory Committee Meeting, the panel did not recommend approval of OME-Mg for OTC use. The AC Recommendations on The Risk-Benefit (Approval) Question are summarized in Table 1.

**TABLE 1**  
**NDA 21-229**

**October 20, 2000 Advisory Committee's Recommendations on  
The Risk-Benefit (Approval) Question  
# of Voting Members = 13**

| Indication                                                                                                                                                                                                          |                           | NO <sup>a</sup> | YES <sup>b</sup> | ABSTAIN |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-----------------|------------------|---------|
| <b>A. OME-Mg 10 mg</b>                                                                                                                                                                                              |                           |                 |                  |         |
| I.                                                                                                                                                                                                                  | Acute Symptomatic HB      | 11              | 2                | 0       |
| II.                                                                                                                                                                                                                 | Prevention of Episodic HB | 10              | 2                | 1       |
| III.                                                                                                                                                                                                                | Treatment of Chronic HB   | 9               | 3                | 1       |
| <b>B. OME-Mg 20 mg</b>                                                                                                                                                                                              |                           |                 |                  |         |
| IV.                                                                                                                                                                                                                 | Acute Symptomatic HB      | 11              | 2                | 0       |
| V.                                                                                                                                                                                                                  | Prevention of Episodic HB | 10              | 2                | 1       |
| VI.                                                                                                                                                                                                                 | Treatment of Chronic HB   | 9               | 3                | 1       |
| a) NO means that there is not sufficient evidence of demonstration of efficacy/safety for use in an OTC setting.<br>b) YES means that the risk/benefit ratio is acceptable for the OTC setting to support approval. |                           |                 |                  |         |

In addition to the above-summarized replies to questions, concern was voiced that patients with EE are subsumed in the target patient population, for whom adequate dosing to enable mucosal healing must be given.

In a letter dated June 5, 2001, to the Division Director, P & G proposed to change the indication. The new indication read:

### USES

- "for prevention of frequent heartburn"
- "Intended for those who suffer heartburn two or more days a week."

It is evident that the population<sup>4</sup> targeted by the sponsor overlaps significantly with those individuals that have symptoms that are consistent with the diagnosis of gastroesophageal reflux disease (GERD). As already mentioned, the latter could present as erosive esophagitis (EE; esophageal lesions) or symptomatic GERD (s-GERD; no esophageal lesions). Important management/treatment issues pertaining to GERD patients to be treated with OME-Mg that are relevant to OTC availability of the drug should be addressed by the AC. It is important to note that GERD is a **chronic relapsing condition** that subsumes patients with recurrent symptoms and or mucosal erosions/ulcerations that require an adequate duration of treatment of inflammation. In outpatient settings, a 4 to 6 week initial course of adequate dosing with a PPI is usually prescribed.

Issues surrounding OTC usage of OME-Mg to treat frequent heartburn were discussed in detail by the Medical Team Leader in a memorandum dated October 23, 2000. Listed among the favorable consequences were:

- With adequate information and the proper education, the consumer might be able to differentiate episodic (occasional) HB, the symptom, from GERD-associated HB, and proceed to self-medicate him/herself with either antacids/H<sub>2</sub>s or OME-Mg.
- No initial endoscopy is needed before self-medication begins (in addition to cost, endoscopy is unpleasant and is associated with some risk).
- Follow-up endoscopy for esophagitis is generally unnecessary and is restricted to the patient whose symptoms fail to respond to therapy, who has an esophageal ulcer, or for whom additional biopsy and cytologic studies are needed to clarify the diagnosis [ASGE Publication No. 1006: *Guidelines for Clinical Application. The Role of Endoscopy in the Management of GERD*, Revised December 1998].
- "Most HB sufferers do not bother to visit a doctor with their complaints" [D. Y. Graham, *Dig. Dis. Sci.* 29:589-590 (1984)].
- "Most proprietary antacid tablet use is a reflection of reflux esophagitis" [D. Y. Graham, *Amer. J. Gastroenterol.* 78: 257-260 (1983)].
- "Masking of important disease is unlikely in the context of short-term usage, if properly labeled" [Dr. D. Castell, at the October 20, 2000 AC meeting].

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<sup>4</sup> At the October 20, 2000 AC, Dr. William M. Steinberg stated (page 356 of the AC meeting transcript): "In my mind there is no difference between GERD and chronic heartburn"

- The consumer might be able to identify clinical clues that suggest that reflux may be severe or that other diseases may be present (dysphagia, odynophagia, persistent symptoms in spite of therapy, extra-esophageal symptoms of GERD, esophageal symptoms in an immunosuppressed patient, overt gastrointestinal bleeding). For these conditions, proposed OTC labeling instruct him/her to see a physician which will likely pave the way for an endoscopic examination.
- "This approach may bring HB patients to physicians" [Dr. D. Castell, at the October 20, 2000 AC meeting].

Listed among unresolved issues or undesirable consequences in an OTC setting were:

- determination of the adequate dose to suppress symptoms and effectively treat EE;
  - establishment of the minimal required duration of administration to effectively treat consumers;
  - the impracticability of treating GERD (whether symptomatic GERD or erosive esophagitis) over a single short-term treatment course (due to high recurrence rates);
  - lingering concerns about safety that may not be possible to address adequately in the labeling;
  - inappropriate use of the drug in adolescents and younger children;
  - absence of prospective or nested case control trials to characterize potential embryo-fatal damage in humans in view of the clastogenic properties of the drug;
  - potential for masking and/or delaying the diagnosis of GERD complications and malignancy;
  - tumorigenic potential of drug-induced hypergastrinemia associated with long-term usage; and
  - exaggerated rebound of gastric acid secretion and recurrence of esophageal lesions upon drug discontinuation.
  - Another concern is whether the availability of omeprazole-Mg in an OTC setting would delay or prevent consumers from appropriate contact with their physicians.
- 
-

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**III. New Proposal (April 9, 2002)**

In a letter dated April 9, 2002 to the Acting Director of HFD-180, the sponsor listed the following specific items:

**OTC Proposition:**

**Intended Population:** Consumers with frequent heartburn (2 or more days per week)

**Dose:** 20.6 mg omeprazole magnesium (equivalent to 20 mg omeprazole)

**Indication:** for the prevention of the symptoms of frequent heartburn for 24 hours

**Use Directions:** for prevention of frequent heartburn, swallow 1 tablet with a glass  
of water in the morning.

- take every day for 14 days

- do not take beyond 14 days unless directed by your doctor

**Consumer Background/Need:**

- 1) Description of how the drug fits into OTC therapy for heartburn.
- 2) The consumer benefits from OTC omeprazole.

**Efficacy:** According to the sponsor, the data that support efficacy will be limited to the two studies in which subjects dosed daily, for 14 days, to prevent heartburn for 24 hours (Studies 171 and 183).

**NOTE:** Results of these studies are summarized at the end of the present memorandum (in Sections IV and V).

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**Dose:** P&G are proposing a 20.6 mg omeprazole magnesium (equivalent to 20 mg omeprazole) dose. According to the sponsor, the support for this proposal is as follows:

- 1) Pharmacodynamic data show a more consistent acid suppression profile at 20 than at 10 mg.
- 2) 20 mg provided a directionally higher level of prevention across all temporal variables than 10 mg, and in the case of some efficacy endpoints, 20 mg was statistically more effective than 10 mg in two efficacy studies.

The sponsor \_\_\_\_\_ at the AC meeting. The data \_\_\_\_\_ will be included in their briefing document.

**Duration:** P&G is proposing a **14-day duration of consecutive daily dosing**. Clinical efficacy data from the OTC trials and consumer use from the Actual Use trial will be provided. The question of undertreatment of undiagnosed erosive esophagitis will be addressed as part of the basis for 14 days of use.

**Safety:** P & G notes that the previous AC provided positive assessments of short and long-term safety of omeprazole. The unresolved issues related to uncertainty of omeprazole use without physician supervision identified in the 27 November 2000 Action Letter will be addressed (rebound, drug-drug interaction, unintended use during pregnancy/nursing, and unintended use in pediatrics). Additionally, postmarketing data for Ome-Mg and Actual Use trial data will be provided.

The sponsor does not plan to provide detailed safety data beyond these issues.

Also addressed will be issues of label comprehension (new), actual use trial (2001007) and appropriateness of OTC use.

**The joint AC is scheduled for June 21, 2002.**

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**IV. 24-h Prevention: Results of Studies 171 and 183 (Table 2 and 3)**

**Design:** randomized; double-blind, multicenter, placebo-controlled

**Initial Comments:** by FDA on these studies

- **New Indication:** 24h prevention of symptoms for up to 14 days (**Prevention of further heartburn episodes**)
- The MTL believes that for a large proportion of consumers, this new indication represents *management of GERD*.

**Entry Criteria**

- HB of greater than 1 month duration; frequency: at least 2 days per week
- Antacid or OTC H<sub>2</sub>RA responsive HB in the past (enriched population)

**Demographics**

- 80% of subjects: baseline frequency  $\geq$ 50% of days
- Mean severity 1.5 (2=moderate severity)

**Note:** This is a 1→4 scale; the high score is the more severe.

**RESULTS**

Results of primary efficacy variable, *proportion of subjects with NO HEARTBURN* over 24h are shown in Tables 2 (Day 1 the primary endpoint of efficacy) and 3 (Day 14, a secondary endpoint of efficacy).

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**TABLE 2**

**24-h Prevention of HB Following the First Dose**

|            |                | OME -Mg        |                |                    | Therapeutic gain/[p-value] |                 |  |
|------------|----------------|----------------|----------------|--------------------|----------------------------|-----------------|--|
| Study 171  |                |                |                |                    |                            |                 |  |
|            | PL<br>[n=519]  | 10<br>[n=518]  | 20<br>[n=523]  | 10<br>vs<br>PL     | 20<br>vs<br>PL             | 20<br>vs<br>10  |  |
| Responder  | 169<br>(32.6%) | 215<br>(41.5%) | 260<br>(49.75) | 8.9%<br>[0.003]    | 17.1%<br>[<0.001]          | 8.2%<br>[0.008] |  |
| Study 183  |                |                |                |                    |                            |                 |  |
|            | [n=520]        | [n=520]        | [n=524]        |                    |                            |                 |  |
| Responders | 167<br>(32.1%) | 235<br>(45.2%) | 245<br>(46.8)  | 13.1%<br>[1<0.001] | 14.8%<br>[<0.001]          | 1.6%<br>[N.S.]  |  |

**TABLE 3**

**Analysis of Efficacy Variables on Day 14<sup>a</sup>**

| Study                                                | PL    | OME-Mg (mg/d) |       | Therapeutic gain/p-value |                   |                 |
|------------------------------------------------------|-------|---------------|-------|--------------------------|-------------------|-----------------|
|                                                      |       | 10            | 20    | 10<br>vs<br>PL           | 20<br>vs<br>PL    | 20<br>vs<br>10  |
| A. No Heartburn over 24h <sup>b</sup>                |       |               |       |                          |                   |                 |
| 171                                                  | 42.7% | 71.7%         | 69.7% | 29.0%<br>[<0.05]         | 27.0%<br>[< 0.05] | -2.0%<br>[N.S.] |
| 183                                                  | 43.0% | 66.4%         | 73.0% | 23.4%<br>[<0.05]         | 30.0%<br>[<0.05]  | 6.6%<br>[<0.05] |
| B. No Nocturnal Heartburn <sup>c</sup>               |       |               |       |                          |                   |                 |
| 171                                                  | 75.9  | 87.7%         | 86.5% | 11.8%<br>[<0.05]         | 10.6%<br>[< 0.05] | -1.2%           |
| 183                                                  | 80.0% | 83.5          | 88.8  | 3.5%<br>[N.S.]           | 8.8%<br>[< 0.05]  | 5.3%<br>[<0.05] |
| C. No More Than Mild Heartburn Over 24h <sup>d</sup> |       |               |       |                          |                   |                 |
| 171                                                  | 79.6% | 92.2%         | 89.8% | 12.6%<br>[< 0.05]        | 10.2%<br>[< 0.05] | -2.4%<br>[N.S.] |
| 183                                                  | 77.0% | 89.3%         | 92.2% | 12.3%<br>[< 0.05]        | 15.2%<br>[< 0.05] | 2.9%<br>[N.S.]  |

a) Last evaluation of double-blind medication within the Interval Day 14 ± 2.

b, c, d) Percentage of subjects with indicated outcome. Treatment difference tested using Cochran-Mantel-Haenszel Chi-square test with Investigator as a stratification variable.

Note: For both trials, 171 and 183, the Primary Efficacy Endpoint was No HB over 24 hours on Day 1

Based on these results it is apparent that

- there is a substantial proportion of subjects who experience no heartburn despite treatment with placebo, both on Days 1 and 14 (Day 1, study 171 = 32.6%, study 183 = 32.1%; Day 14, study 171 = 42.7%, study 183 = 43%).
- although, statistically significant, the therapeutic gain of OME-Mg 20 mg vs placebo is modest on Day 1 (study 171 = 17.1%; study 183 = 14.8%)
- the therapeutic gain of OME-Mg 20 mg vs placebo increases on Day 14 (study 171 = 27%, study 183 = 30%) confirming that the maximal PD benefit of treatment relies on consecutive dosing.
- even after 14 days of treatment with OME-Mg 20 mg approximately 30% of patients experience "breakthrough" heartburn on Day 14.
- using *No heartburn over 24h* as the parameter of comparison, there is little and at times no difference between responses to 20 vs 10 mg OME-Mg. Study 183 showed N.S. difference between these two dose levels, on Day 1 of treatment (Table 2). Similarly, Study 171 showed N.S. difference between these two doses, on Day 14 of treatment (Table 3).

The proportion of subjects with No heartburn based on heartburn frequency during the run-in period (a measure of GERD severity at baseline) is shown in Tables 4 and 5, taken from the sponsor's submission.

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**Table 4**

8.7 Integrated Summary of Effectiveness

**TABLE 268**  
**PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 1**  
**BY HEARTBURN FREQUENCY (% OF DAYS) DURING RUN-IN**  
**(COMBINED DATA FROM STUDIES 171 AND 183)**

**MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY**  
**INTENT-TO-TREAT SUBJECTS**

| Frequency<br>(% of Days) | Ome-Mg 20        |                |                   | Ome-Mg 10        |                |                   | Placebo          |                |
|--------------------------|------------------|----------------|-------------------|------------------|----------------|-------------------|------------------|----------------|
|                          | n/m <sup>a</sup> | % <sup>b</sup> | Diff <sup>c</sup> | n/m <sup>a</sup> | % <sup>b</sup> | Diff <sup>c</sup> | n/m <sup>a</sup> | % <sup>b</sup> |
| <50%                     | 140/202          | 69.3           | 3.8               | 134/200          | 67.0           | 1.5               | 131/200          | 65.5           |
| 50%-74%                  | 173/302          | 57.3           | 15.4              | 166/298          | 55.7           | 13.8              | 124/296          | 41.9           |
| 75%-99%                  | 97/200           | 48.5           | 22.4              | 75/197           | 38.1           | 12.0              | 47/180           | 26.1           |
| 100%                     | 93/343           | 27.7           | 18.3              | 75/343           | 21.9           | 12.5              | 34/363           | 9.4            |

<sup>a</sup> Number of subjects with no heartburn over 24 hours/Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.  
<sup>b</sup> Percentage of subjects with no heartburn over 24 hours.  
<sup>c</sup> Difference between treatment percent and placebo percent.  
 Note: See Appendix 2.1.5 of Section 8.7 for supporting documentation.

**Table 5**

**PERCENTAGE OF SUBJECTS WITH NO HEARTBURN OVER 24 HOURS ON DAY 14 BY**  
**HEARTBURN FREQUENCY (% OF DAYS) DURING RUN-IN**  
**(COMBINED DATA FROM STUDIES 171 AND 183)**

**MULTIPLE-DOSE PREVENTION STUDIES: HEARTBURN SYMPTOMS OVER A FULL DAY**  
**INTENT-TO-TREAT SUBJECTS**

| Baseline<br>HB Freq<br>(% of days) | Ome-Mg 20        |                |                   | Ome-Mg 10        |                |                   | Placebo          |                |
|------------------------------------|------------------|----------------|-------------------|------------------|----------------|-------------------|------------------|----------------|
|                                    | n/m <sup>a</sup> | % <sup>b</sup> | Diff <sup>c</sup> | n/m <sup>a</sup> | % <sup>b</sup> | Diff <sup>c</sup> | n/m <sup>a</sup> | % <sup>b</sup> |
| <50%                               | 165/195          | 84.6%          | 11.4              | 164/198          | 82.8%          | 9.6               | 142/194          | 73.2%          |
| 50%-74%                            | 227/295          | 76.9%          | 24.0              | 229/294          | 77.9%          | 24.9              | 153/289          | 52.9%          |
| 75%-99%                            | 132/194          | 68.0%          | 33.8              | 136/195          | 69.7%          | 35.5              | 61/178           | 34.3%          |
| 100%                               | 204/336          | 60.7%          | 38.6              | 178/337          | 52.8%          | 30.7              | 78/352           | 22.2%          |

<sup>a</sup> Number of subjects with no heartburn over 24 hours/Number of Intent-to-Treat subjects represented in subgroup. Note: In this analysis, subjects with missing data are assumed to have heartburn.  
<sup>b</sup> Percent of subjects with no heartburn over 24 hours for last day of dosing (Day 14 ± 2 days). Subject is excluded if last evaluation is prior to Day 12. Day 16 is used if last evaluation exceeds this day.  
<sup>c</sup> Difference between treatment percentage and placebo percentage.

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Based on these results:

- in each of the baseline heartburn frequency categories the proportion of responders to OME-Mg increases between Day 1 and 14.
- the proportion of OME-Mg responders is higher in subjects with low compared to high frequency heartburn at baseline.
- there is a substantial treatment failure rate after 14 Days in subjects with high frequency heartburn at baseline (about 40% of subjects with 100% heartburn frequency at baseline treatment with an OME-Mg dose of 20 mg, and almost 50% of subjects with 100% heartburn frequency at baseline treated with an OME-Mg dose of 10 mg).
- the therapeutic gain of OME-Mg vs placebo in subjects with low frequency heartburn at baseline is very small but is more substantial in those with high frequency heartburn at baseline.

After cessation of treatment with OME-Mg (14 days course) the recurrence of heartburn was rapid. As shown in Table 6, 50% of recurrences occurred within 3 days and 75% within 5 days at a daily dose of 20 mg, and recurred somewhat sooner at a daily dose of 10 mg.

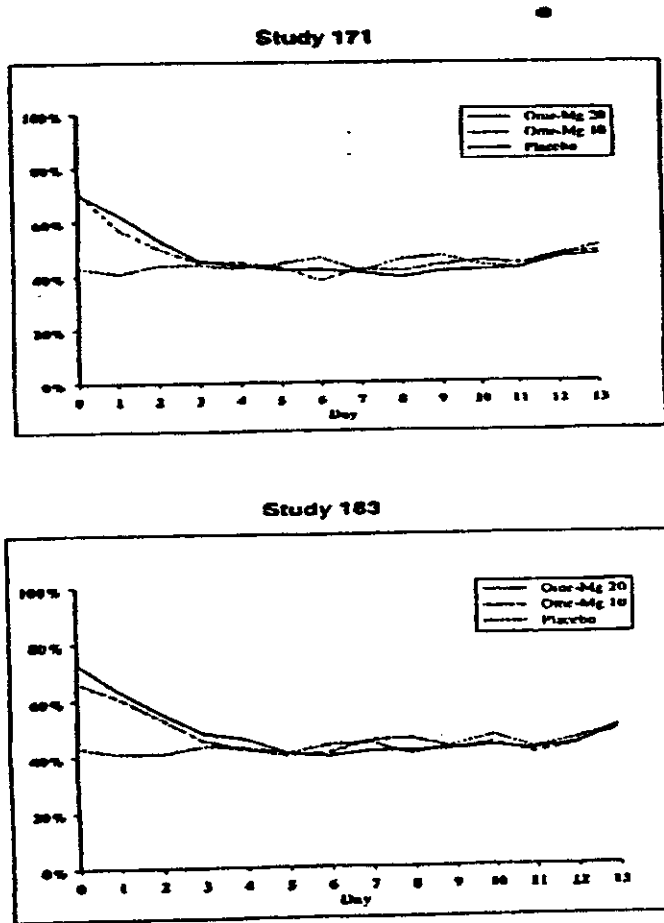
**Table 6**

| TABLE 31<br>NUMBER OF DAYS TO FIRST OCCURRENCE OF HEARTBURN DURING FOLLOW-UP PHASE<br>(AFTER TWO WEEKS DAILY DOSING)<br>PER-PROTOCOL SUBJECTS |                                          |     |                                          |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-----|------------------------------------------|-----|
|                                                                                                                                               | 50 <sup>th</sup> Percentile <sup>a</sup> |     | 75 <sup>th</sup> Percentile <sup>a</sup> |     |
|                                                                                                                                               | 171                                      | 183 | 171                                      | 183 |
| Ome-Mg 20                                                                                                                                     | 3                                        | 3   | 5                                        | 5   |
| Ome-Mg 10                                                                                                                                     | 2                                        | 3   | 4                                        | 5   |
| Placebo                                                                                                                                       | 1                                        | 1   | 3                                        | 3   |

<sup>a</sup> Estimated using Kaplan-Meier method.  
Note: Information in this table is extracted from Table 8.2.16 in the Clinical Study Reports 171 and 183.

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As shown in Fig. 1 [Upper panel = study 171; lower panel = study 183], after cessation of treatment with OME-Mg within 3 days the apparent therapeutic gain compared to placebo **disappears**. Thus, **rapid loss of heartburn prevention effect** in the OME-Mg-treated population, with approximately 60% of subjects experiencing heartburn on any successive day demonstrates a pattern of symptoms *consistent with GERD*. This important finding must be reconciled with the proposed labeling that assumes subjects will only self medicate for one 14-day period.



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\* Note: Day 0 is last evaluation of double-blind medication.

Figure 1

Percentage of Subjects with No Heartburn over 24 Hours  
by Day<sup>a</sup> after end of Double-Blind Phase  
Per Protocol Subjects who enter Follow-Up Phase

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V. Brief Summary of Results/Conclusions

**Daily Dose 24-Hour Prevention Studies**

- Replicated statistically significant difference compared to placebo
- Efficacy at both dose levels
- Efficacy increases over time

**Day 1: Therapeutic gain 9 to 17%**

**Day 14: Therapeutic gain 23 to 30%**

- Successful prevention of HB symptoms with 10 mg and 20 mg dose levels
- Inconsistent (and/or small) differences between OME-Mg 10 vs 20 mg
- Increased efficacy over time
- Benefit lost within 3 days of discontinuation
- Only study 171 showed superiority of OME-Mg to placebo in the 2-week prevention of nocturnal HB.
- Long-term patterns of HB recurrence are not addressed in the two studies identified by the sponsor as critical.

VI. Unresolved issues

1. How is the consumer going to differentiate OME-Mg, a product without efficacy for single dose acute treatment of episodic heartburn, from antacids and H<sub>2</sub>-receptor antagonists?
2. Whereas a certain proportion of patients within the target population (individuals with frequent heartburn) will have GERD with/without erosive esophagitis, there is need to determine the adequate dose (10 vs 20 mg) and duration of treatment (28 vs 14 days) to suppress symptoms and b) effectively treat esophageal lesions in an OTC setting.

3. Clarification of whether it is important that consumers do not going to take OME-Mg chronically or for **maintenance purposes** without consulting a physician. Due to high **recurrence rates** of symptoms and esophageal lesions in patients with GERD, it is impractical to treat individuals with this condition (whether s-GERD or erosive esophagitis) with a single 14-day course of treatment.
4. If consumers self-medicate with **more than one treatment course per year**, how many treatment courses are acceptable (per user)?
5. Clarification of the appropriate and safe use of the drug in adolescents and younger children.
6. An additional concern is whether the availability of omeprazole-Mg in an OTC setting would delay or prevent consumers from appropriate contact with their physicians.

ISI

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Hugo E. Gallo-Torres, M.D., Ph.D.  
Medical Team Leader  
HFD-180

cc:

NDA 21,229

HFD-180

HFD-180/VRaczkowski

HFD-180/JKorvick

HFD-103/FHoun

HFD-560/CGanley/LKatz/DKeravich

HFD-005/Bull

HFD-180/HGallo-Torres

HFD-180/MAvigan

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MEDICAL OFFICER

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## MEMORANDUM OF TELECON

DATE: April 17, 2002 .

APPLICATION NUMBER: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Linda Jones, Regulatory Affairs  
Phone: (513) 622-3176  
Representing: Proctor and Gamble Co.

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Correction to IR letter dated 4/16/02

**BACKGROUND:** An information request (IR) letter was issued to Proctor and Gamble on 4/16/02 requesting additional information regarding the clinical section of the resubmission of NDA 21-229 dated 2/12/02. Karen Lechter called me today and pointed out that the requests (under item #1) for: a) a copy of the recruitment screener, questionnaire, and script; and b) a copy of any materials the participants were exposed to, including oral and written materials, actually pertain to Heartburn De-Selection Qualitative Research (US017859/USO18387) and not to Label Comprehension Study Number 12179 as stated in the IR letter.

**TODAY'S CALL:** I called Ms. Jones and relayed the above correction to the IR letter. She stated the sponsor's response to the letter will provide the requested information from the de-selection study and not the label comprehension study. The call was then concluded.

*/s/*

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Maria R. Walsh, M.S.  
Regulatory Project Manager

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NDA 21-229

INFORMATION REQUEST LETTER

The Procter and Gamble Co.  
Attention: William Kozarek, Ph.D.  
Section Head, Regulatory Affairs  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

16- APRIL-2002

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We also refer to your submission dated February 12, 2002, which constituted a complete response to the November 27, 2000 action letter.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the Label Comprehension Study Number 12179, please provide the following information:
  - a) A copy of the recruitment screener, questionnaire, and script.
  - b) A copy of any materials the participants were exposed to, including oral and written materials.
2. Regarding the Heartburn De-Selection Qualitative Research (US017859/US018397), please provide the following information:

A photograph or drawing of the display from which the participants chose the product they would use, including a view of the shelf tag saying "New! For Frequent Heartburn" and any other shelf tags used in the study.
3. Regarding Studies 171 and 183, both entitled, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Investigate the Safety and Efficacy of Omeprazole, 10 mg QD and 20 mg QD, in Preventing Heartburn":

In the Integrated Summary of Efficacy (ISE) in the January 27, 2000 submission, Table 26B demonstrates the "Percentage of subjects with no heartburn over 24 hours on DAY 1 (of treatment) by heartburn frequency (% of days) during run-in (combined data from studies 171 and 183).

Please provide similar data on the "Percentage of subjects with no heartburn over 24 hours on DAY 14 (of treatment) and during active treatment phase by heartburn frequency (% of days) during run-in (combined data from studies 171 and 183).

If you have any questions, call Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Julieann DuBeau, RN, MSN  
Chief, Project Management Staff  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

APR 19 2002

**Office of Drug Safety**

# Memo

**To:** Victor Raczkowski, M.D.  
Acting Director, Division of Gastro-Intestinal and Coagulation Drug Products  
HFD-180

**From:** Alina R. Mahmud, R.Ph.  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-400

**Through:** Carol Holquist, R.Ph.  
Deputy Director, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-400

Jerry Phillips, R.Ph.  
Associate Director, Office of Drug Safety  
HFD-400

**CC:** Maria Walsh  
Project Manger  
HFD-180

**Date:** April 3, 2002

**Re:** ODS Consult 00-0081-1; Prilosec 1 (Omeprazole Tablets) 20 mg; NDA 21-229.

---

This memorandum is in response to a February 13, 2002, request from your Division for a review of the sponsor's comments in reference to OPDRA consult 00-0081 dated October 30, 2000, in which DMETS did not recommend the use of the proprietary name Prilosec 1. In addition, revised labels and labeling were provided to DMETS for review and comment.

## I. PROPRIETARY NAME

The proprietary name, Prilosec, was approved for Omeprazole Delayed-Release Capsules under NDA 19-810. The NDA was initially approved on September 14, 1989, with the proprietary name, Losec. In 1991, the name was changed to Prilosec due to reports of medication errors resulting from proprietary name confusion. The sponsor, AstraZeneca, submitted a new NDA for an Over the Counter (OTC) formulation of Omeprazole and has proposed to use the proprietary name, Prilosec 1. This new dosage form (Tablet) contains the active ingredient Omeprazole magnesium rather than Omeprazole. Prilosec 1 will be marketed as a 20 mg tablet in cartons containing \_\_\_\_\_ count tablets.

OPDRA conducted a review of the proposed proprietary name "Prilosec 1" on October 30, 2000. *OPDRA did not recommend the use of the proposed proprietary name from a safety perspective and DDMAC found the name objectionable from an advertising and promotional perspective (see OPDRA consult 00-0081).* In addition, label and labeling comments were provided to the sponsor. The sponsor has submitted the following comments in response to our recommendations outlined in the initial consult:

### Sponsor's comments:

The proposed OTC trade name is Prilosec 1. The suffix "1" was chosen to reinforce with the consumers they should take only 1 tablet per day and 1 tablet per dose. As Prilosec 1 will be classified with the other acid reducers (e.g., H<sub>2</sub>-receptor antagonists) that can be dosed up to 2 times per day, we wanted to reinforce the message that only one tablet can be taken per day. The Prilosec 1 tradename is consistent with this message and results of our Label Comprehension (Study No. 02255) and Actual Use (Study No. 2001007) Studies show a very high understanding and compliance to one tablet per dose and one tablet per day dosing.

### DMETS comments:

DMETS discourages the use a numeric suffix in conjunction with the proprietary name because suffixes have often been misinterpreted as the product strength or the number of tablets to be administered. The sponsor states that the modifier "1" was chosen to distinguish Prilosec 1 from other currently marketed OTC acid reducers; however, *the recommended dose of the currently marketed acid reducers is one tablet daily.* One tablet may be taken twice daily if needed. The sponsor is clearly misleading patients because two tablets are not always necessary to achieve relief with the other acid reducers. In addition, consumers should be discouraged from relying on modifiers to identify important information, such as the dosing regimen, about a drug product. Furthermore, the statement "\_\_\_\_\_ on proposed container labeling *clearly* conveys the dosing regimen to consumers whereas the modifier "1" does not. The use of the modifier "1" suggests a superiority about the drug product meaning it is "first" or "best". DMETS can not comment on the studies performed by the sponsor as the methodology of these studies were not provided for evaluation.

**Sponsor's comments:**

The Agency has commented about the potential of confusion with prescription Prilosec. We believe the risk of any potential confusion of the OTC Prilosec 1 product and name with the prescription product and name will be minimal. Significant physician and pharmacist education will be conducted prior to consumer availability. The effort will increase name recognition and label awareness to significant levels via in-office detailing, direct mail and broad awareness advertising. As a result brand name awareness as well as dosage strength and indications will be well understood by the professional community prior to retail distribution.

**DMETS comments:**

We acknowledge and encourage the sponsor's initiatives in educating healthcare professionals and consumers on the proposed product and name prior to the product being marketed. However, we are concerned about medication errors that may occur with the use of the modifier "1" especially since numerous study participants from the prescription studies (see OPDRA consult 00-0081) interpreted "Prilosec 1" as "Prilosec" and Prilosec 10 mg, available by prescription, differs in script from "Prilosec 1" by the number zero. The number "1" in conjunction with the proprietary name was misinterpreted as the strength "10 mg". DMETS is also concerned that the proprietary name and strength when scripted as "Prilosec 1 20mg" could also be misinterpreted as "Prilosec 120 mg" where the strength may read as 120 mg instead of 20 mg. Similarly, a verbal order for "Prilosec 1-20 mg" may also be misinterpreted as 120 mg. A dose of 120 mg once daily (and up to three times daily) is not unusual as it can be prescribed for certain hypersecretory conditions. Although the intended drug product Prilosec 1 is an over-the-counter medication, prescriptions may be written for health insurance purposes (prescriptions are routinely written for Medicaid patients), patient reminders, or pharmacy procedural requirements for all products including prescription and over-the-counter medications (Military hospitals and clinics, Veteran's Medical Centers, Long Term Care and Managed Care facilities). In addition, OTC medications are frequently written on inpatient pharmacy orders in hospitals.

**Sponsor's comments:**

The Agency's greatest concern is most likely the misfilling of a prescription. We believe the potential for misfilling a prescription with the OTC product (and vice versa) will be very rare and the consequences of any misfilling will be minor, if any. First, the likelihood that physicians will write a prescription for an OTC product is rare. Second, all prescriptions are required to specify the specific product name, dose and quantity of the product. As described in the chart below, there are significant packaging and quantity differences that will clearly delineate the OTC product from the prescription product. In addition it is current standard practice of pharmacists to call the prescribing physician and to clarify any questions about the prescription. Lastly, since the vast majority of the prescriptions are for 20 mg omeprazole capsules and the proposed OTC dose is also 20 mg, misfilling a prescription with the OTC product is highly unlikely to result in any significant consequences.

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**DMETS comments:**

The likelihood that physicians will write a prescription for an OTC product is not rare. Prescriptions may be written for health insurance purposes (such as Medicaid), patient reminders, or pharmacy procedural requirements for all products including prescription and over-the-counter medications (Military hospitals and clinics, Veteran's Medical Centers, Long Term Care and Managed Care facilities). In addition, OTC medications are frequently written on inpatient pharmacy orders in hospitals. Although all prescriptions are required to specify the specific product name, dose and quantity of the product, real life prescribing and dispensing practices do not always occur in this manner. Post-marketing experience has shown written prescriptions lacking modifiers, strengths, quantities, and directions for use. In addition, even when all the above mentioned factors are present, dispensing errors occur because a pharmacist rushes to fill the prescription. We acknowledge the sponsor's efforts in creating significant packaging differences to delineate the OTC product from the prescription product; however, packaging differences will not aid a pharmacist in correctly filling a prescription if the prescription is misread. A pharmacist may not call the physician for clarification on a prescription if a prescription for "Prilosec 1" is misread as "1" (or vice versa) especially since the dosing regimens are identical. Consequently, the patient will receive half the intended dose. Filling the OTC product with the 20 mg prescription strength product may not result in significant consequences; however, the use of the modifier "1" in Prilosec 1 may introduce dosing errors (as described above) which will result in the patient receiving either more or less of the intended dose.

**II. LABELING, PACKAGING AND SAFETY RELATED ISSUES**

In the review of the revised container label, carton and package insert labeling for "Prilosec 1", DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified some areas of possible improvement, in the interest of minimizing potential user error.

**A. GENERAL COMMENT**

The word "new" should be deleted from the labels and labeling unless the sponsor plans on submitting revised labels and labeling (without the term "new") six months post marketing to replace the proposed labels and labeling. The term "new" may be used on labels and labeling for a period not to exceed 6 months.

**B. BLISTER CARD**

Relocate the established name to appear in conjunction with the proprietary name. For example, the term "acid reducer" appears immediately beneath the proprietary name; however, this should be relocated so that the established name appears immediately beneath the proprietary name.

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C. CARTON LABELING (DIRECTIONS)

The following statements should also be bolded to increase their prominence:

- Do not take more than 1 tablet a day
- Do not chew or crush tablets

D. PACKAGE INSERT

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In summary, DMETS does not recommend the proposed proprietary name "Prilosec 1". DMETS recommends the use of the nomenclature currently utilized by other OTC acid reducers (e.g., Pepcid AC and Axid AR). In addition, we recommend the implementation of the labeling revisions outlined in section II of this memo.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

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Alina Mahmud  
4/18/02 10:42:37 AM  
PHARMACIST

Carol Holquist  
4/18/02 03:57:13 PM  
PHARMACIST

Jerry Phillips  
4/19/02 08:50:24 AM  
DIRECTOR

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ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Walsh

Food and Drug Administration  
Rockville MD 20857

Joseph M. Gautreaux, III, M.D.  
4740 South I-10 Service Road  
Suite 310  
Metairie, Louisiana 70001

MAR 25 2002

Dear Dr. Gautreaux:

Between January 30 and February 26, 2001, Ms. Barbara Wright and Ms. Donna Gallien, representing the Food and Drug Administration (FDA), met with you to investigate allegations of regulatory noncompliance and to review your conduct of the following clinical studies:

[REDACTED]

Protocol P&G 1997087 entitled "A Multicenter, Double-Blind, Randomized, Single-Dose, Placebo-Controlled Study to Investigate the Efficacy and Safety of 20 mg Omeprazole in Preventing Meal-Induced Heartburn Symptoms Following a Provocative Meal," performed for Procter and Gamble.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you were in basic compliance with pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects for the studies for which you were the principal investigator.

[REDACTED]

We appreciate the cooperation shown Investigators Wright and Gallien during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[ 159 ]

Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD-46/47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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CFN: \_\_\_\_\_

Field Classification: OAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why: \_\_\_\_\_

\_\_\_\_\_ Protocols \_\_\_\_\_  
1997087 were acceptable.

cc:

HFA-224

HFD-180 Doc. Rm.: IND # 54307

HFD-180 MO Gallo Torres

HFD-180 PM Walsh

HFD-180 Review Division Div. Dir. Talarico

HFD-46/47 c/r/s GCP file #10326

HFD-47 El-Hage

HFD-46/47(RS/KS)

HFR-SE450 DIB Debo

HFR- SE450 BIMO Monitor Wright

HFR- SE450 Field Investigator Wright/Gallien

O:\RS\SPQR\GautreauxNAI.doc

r/d:(RS/3/13/02)

f/t:(MB:3/15/02)

o:\RS\SPQR\GautreauxNAI.doc

**Reviewer Note to Rev. Div. M.O.**

While data submitted for protocols \_\_\_\_\_ and P&G 1997087 did not have significant regulatory violations, \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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/s/  
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Maria Walsh  
2/26/02 01:19:10 PM

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ON ORIGINAL



Colin G. Bailey, M.D.  
735 West Fifth Street  
LaPlace, Louisiana 70068

Food and Drug Administration  
Rockville MD 20857

MAR - 1 2002

Dear Dr. Bailey:

Between November 29, 2000 and February 22, 2001, Ms. Barbara Wright and Ms. Donna Gallien, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # AMI-171) of the investigational drug omeprazole, performed for Astra Merck Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written responses dated March 7 and 8, 2001, we conclude that you did not adhere to federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, our personnel presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. Your written responses of March 7 and 8, 2001 explain the circumstances that caused the departures from FDA regulations. We accept your responses and wish to emphasize the following:

1. You did not personally conduct or supervise the clinical investigation in that you did not know your sub-investigators and you visited the research site only 4 times although 127 subjects were enrolled. We remind you that as the principal investigator of record, you are responsible for personally conducting or supervising the clinical investigation.
2. You did not list \_\_\_\_\_ as a sub-investigator until July 9, 1998 although he had examined/enrolled subjects since March 19, 1998.
3. You did not conduct the study in accordance with the relevant, current protocol in that you treated/examined subjects 007, 008, 027, 071, 072 and 073 outside the protocol-specified time period.
4. You did not maintain adequate and accurate study records in that the medical histories were inconsistent for subjects 085, 087 and 099, who participated in multiple studies. In addition, the case report forms for subjects 060 and 063 did not report prior/concomitant medications.

We trust, as you stated, that corrective measures have been instituted to prevent similar problems in your current studies. We note your stated intent to not participate in future clinical trials due to your private practice demands. Your response will be included as a permanent part of your file. If information is requested in accordance with the Freedom of Information Act, our response will include all the related correspondence in your file; this will serve to give a more complete picture of the inspection report.

Page 2 – Colin G. Bailey, M.D.

Please be advised that we plan to monitor your activities to ensure that you have implemented appropriate actions and revised your procedures to comply with federal regulations.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns regarding this letter or investigation, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely yours,

[ 151 ]

Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD-46/47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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Page 3 – Colin G. Bailey, M.D.

FEI: \_\_\_\_\_

Field classification: OAI – WL

Headquarters classification:

- 1) NAI
- 2) VAI-no response required
- 3) VAI-response reviewed and accepted
- 4) OAI - WL 15 day response

**Reason for change in classification:** Investigator's responses of March 7 and 8, 2001 state that this was his first drug study and he did not appreciate the time commitment involved. To quote him, "In the future I probably will not wish to participate in any clinical trials due to time restraints as a result of my private practice." His response also provided that extra efforts and more attention would be made for any future studies to ensure that these violations do not recur. The responses are deemed acceptable.

Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- failure to adhere to protocol
- inadequate records
- failure to report ADRS
- other (specify) Failure to personally conduct or supervise; failure to reimburse subject

Applicable Deficiency Codes: 5, 6, 8, 12, 18

cc:

HFA-224  
HFD-180 Doc. Rm.: IND# 54,307  
HFD-180 MO Kress  
HFD-180 PM Walsh  
HFD-180 Review Div. Dir. Talarico  
HFD-46/47 c/r/s GCP file #10238  
HFD-46/47 Malek/Friend  
HFR-SE450 DIB Debo  
HFR-SE450 BIMO Monitor Wright  
HFR-SE450 Field Investigator Wright & Gallien  
O:BRF/Investigator VAI-RR/Bailey  
r/d: BRF(2/25-26/02:2/27/02)  
reviewed:U(2/26/02)  
reviewed:AEH (2/02)  
f/t:MB(2//02)

Note to Rev. Division M.O. (From Dr. Malek)

This was a "For Cause" inspection that resulted from a complaint by sponsor Astra Pharmaceuticals claiming that one subject never saw a physician and another subject never had any blood drawn, in study protocol # 171 of IND # 54307 where Colin Bailey, M.D. was the PI. Drs \_\_\_\_\_ and Bailey had contractual relationship with a site management

organization ( ) and operated in the same town. DSI conducted "For Cause" inspections for all of them ( ) Dr. Bailey, ( )

Inspection of Dr. Bailey revealed these defects:

- 1) He signed physical examination reports without seeing the subjects.
- 2) Inadequate supervision in the conduct of the study. He admitted visiting the study site only four times although 127 subjects were enrolled.
- 3) Protocol violations
- 4) Inaccurate medical histories and concomitant medications.
- 5) For many subjects in the study, there was no record of medical history or medical condition prior to the study.

Data is not acceptable.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 21-229

26 - FEB - 2002

The Proctor and Gamble Co.  
Attention: Douglas Ws. Bierer, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

Dear Dr. Bierer:

We acknowledge receipt on February 12, 2002 of your February 12, 2002 resubmission to your new drug application (NDA) for Prilosec 1 (omeprazole magnesium) Tablets.

This resubmission contains additional clinical information submitted in response to our November 27, 2000 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is August 12, 2002.

If you have any questions, call me at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

**FACSIMILE TRANSMITTAL SHEET**

**DATE: 02/11/03**

|                                    |                                      |
|------------------------------------|--------------------------------------|
| <b>To: Linda Jones</b>             | <b>From: Melissa Hancock Furness</b> |
| <b>Company: Proctor and Gamble</b> |                                      |
| <b>Fax number: 513-622-1996</b>    | <b>Fax number: 301-443-9285</b>      |
| <b>Phone number: 513-622-3176</b>  | <b>Phone number: 301-827-7450</b>    |
| <b>Subject: NDA 21-229</b>         |                                      |

**Total no. of pages including cover: 1**

**Comments:**

During the review of your pending application, the Agency has noticed that one of the plants listed in your NDA as an alternate Tablet Packaging site has received a \_\_\_\_\_ recommendation from our inspectors as of October 9, 2002. The site is :

[ \_\_\_\_\_ ]

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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/s/

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Melissa Furness  
2/11/03 11:50:41 AM  
CSO

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MEMORANDUM

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

DATE: October 22, 2001

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, HFD-180

SUBJECT: NDA 21-229 [Procter and Gamble (P&G)]  
PRILOSEC 1 [omeprazole (OME) magnesium]  
28 vs 14-day dosing regimen for OTC use

TO: Acting Director, Division of Gastrointestinal and Coagulation Drug Products  
HFD-180

**I. BACKGROUND/INTRODUCTION**

P&G is pursuing approval of PRILOSEC 1, a proton pump inhibitor (PPI), for OTC use.

In their initial submission (January 27, 2000) the sponsor sought to market OTC OME for "acute episodic heartburn" (HB) and proposed the following labeling wording: "relief of HB, acid indigestion and sour stomach and prevention of these symptoms brought on by consuming certain foods and beverages". Upon review of the evidence presented by the sponsor, the GI Team concluded that OME, like all other PPIs, is not suitable for this indication. The indication requires rapid onset of action, which is provided by either acid neutralizers (antacids) or rapidly acting antisecretory drugs (other than PPIs). The H<sub>2</sub>-receptor antagonists (H<sub>2</sub>-RAs) for non-prescription use are taken at a fraction of the approved daily prescription dose.

As part of the background information it is worth summarizing the differences in the PD properties between H<sub>2</sub>s and PPIs. With H<sub>2</sub>s or antacids the onset of maximal effects is relatively rapid and of short duration. Daily doses over a few days, generally do not have increasing or long-lasting effects on acid levels and reduction caused by these agents is neither maximal nor sustained.

On the other hand, adequate acid suppression by the first dose of PPI is not quickly obtained. Pronounced suppression of acid production is obtained only after a few days of daily dosaging although, upon termination of treatment, anti-secretory effects linger for a few days.

At the October 20, 2000 meeting of the Nonprescription Drugs and G.I. Drugs Advisory Committee, concern was voiced that patients with erosive esophagitis (EE) are subsumed in the targeted patient population, for whom adequate dosaging to enable mucosal healing must be given.

**II. NEW PROPOSAL**  
**(including the 14 vs 28 days issue)**

In a letter dated June 5, 2001, to the Division Director, P&G proposed to change the indication. This new indication now reads:

**USES**

- "for prevention of frequent heartburn"
- intended for those who suffer heartburn two or more days a week.

The G.I. Team believes that the population<sup>1</sup> chosen by the sponsor overlaps significantly with those individuals that have symptoms that are consistent with the diagnosis of gastroesophageal reflux disease (GERD). The latter could present as erosive esophagitis (EE; esophageal lesions) or symptomatic GERD (s-GERD; no esophageal lesions). We believe that important clinical management/treatment issues pertaining to GERD patients to be treated with OME need to be thoroughly addressed. It is important to note that GERD is a chronic relapsing condition that subsumes patients with mucosal erosions/ulcerations that require an adequate duration of treatment of inflammation. In outpatient settings, a 4 to 6 week initial course of adequate dosing with a PPI is prescribed.

**i. Adequate dose**

We believe that the adequate dose for the precise indication (either EE or s-GERD) has not been determined.

**ii) The 10 mg once-a-day dose**

This dose may suffice to improve symptoms in both EE and s-GERD patients. However, the effects of this dose level on healing of esophageal lesions needs to be assessed.

**iii) The 20 mg once-a-day dose**

Although this is the approved prescription dose for both GERD indications, the available information suggests that there might be differences in symptomatic response to this OME dose, depending upon whether the patient has EE or s-GERD (PRILOSEC labeling). This issue needs to be further assessed.

**APPEARS THIS WAY  
ON ORIGINAL**

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<sup>1</sup> At the October 20, 2000 AC, Dr. William M. Steinberg stated (page 356 of the transcript):  
"In my mind there is no difference between GERD and chronic heartburn"

iv) 14 vs 28 days of treatment

- Neither of these two lengths of treatment is adequate for the effective treatment of EE (healing of lesions).

Pertinent PRILOSEC Labeling data on healing rates with grading daily doses of OME (which do not include response to 10 mg) are given below. The PPI was administered to patients with symptoms of GERD and endoscopically diagnosed EE of grade 2 or above:

| WEEK | PRILOSEC (mg/day) |              |
|------|-------------------|--------------|
|      | 20<br>[n=83]      | 40<br>[n=87] |
| 4    | 39%               | 45%          |
| 8    | 74%               | 75%          |

The above data mean that at 28 days ca. 60% of the EE patients given OME at the recommended dose of 20 mg/day remain **unhealed**. Thus the 28 days represents a (not that great) compromise.

- Both EE and s-GERD are **chronic conditions** that need to be treated **long-term**, for months or years. Management may include endoscopic assessment for diagnosis, follow-up treatment and to rule out important medical conditions.
- Numerous publications have addressed the impracticability of treating GERD (whether s-GERD or EE) short-term. This was also noted at the October 20, 2000 AC meeting.
- In reality, if OME OTC is approved for 14 days, it is likely that the drug will be used not only for short-term but also for maintenance of healing or maintenance of symptom relief. A pertinent question is what assurance does one have that - having obtained a significant clinical benefit - the patient is going to discontinue taking the drug?.
- If the patient has EE, it is **unrealistic** to expect substantial healing in 14 days, even though these individuals are being treated with a PPI (see above).
- In addition, available comprehension studies with OTC OME strongly suggest that the sponsor is proposing OTC treatment of GERD. This approach presents the opportunities and constraints discussed in detail in Dr. Gallo-Torres' secondary review of October 23, 2000. The GI consultants to the October 20, 2000 AC meeting agreed with Dr. D. Castell's recommendation that GERD may be treated OTC. But **acceptable benchmarks** to facilitate this approach have not been developed. We are left with a series of unanswered questions (among these are those listed under i. through iv. above).

**III. SUMMARY/CONCLUSION**

In summary, the GI Team believes that the proper length of an initial cycle of empirically self-administered treatment of GERD patients is several weeks. The 28 days proposed represents a compromise in that it should be the minimum length of treatment; 14 days treatment is simply too short.

**IV. NEED TO DISCUSS THE 28 vs 14 DAY ISSUE AT AN AC MEETING**

The GI Team also concludes that the 28 vs 14 day length of treatment for OTC GERD is a substantial issue that needs to be considered by an AC.

*/s/*

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Hugo E. Gallo-Torres, M.D., Ph.D.  
Medical Team Leader

cc:

HFD-103/FHoun

HFD-180/VRaczkowski

HFD-180/JKorvick

HFD-180/HGallo-Torres

HFD-180/MAvigan

HFD-181/MWalsh

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Hugo Gallo Torres  
10/25/01 09:27:43 AM  
MEDICAL OFFICER

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NDA 21-229

5-SEP-2001

AstraZeneca LP  
Attention: Gary P. Horowitz, Ph.D.  
Executive Director, Regulatory Affairs  
725 Chesterbrook Blvd.  
Mailstop E-3C  
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec I (omeprazole magnesium) Tablets.

We also refer to your July 6, 2001 submission containing your proposal for resubmission of the safety data in response to the November 27, 2000 not approvable letter. Specifically, you propose to include an updated Safety Update Report containing only outstanding safety information on omeprazole magnesium including an update of the worldwide post-marketing data for omeprazole magnesium (MUPS) tablets and safety data obtained from the Actual Use study (2001007).

We have reviewed your submission and find your proposal acceptable. We remind you that your resubmission must address all the safety issues identified in the not approvable letter.

If you have any questions, call Maria R. Walsh, Regulatory Project Manager, at (301) 443-8017.

Sincerely,

*{See attached electronic signature page}*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Lilia Talarico  
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Walsh

Food and Drug Administration  
Rockville MD 20857

JUN 27 2001

[Redacted]

Dear \_\_\_\_\_

Between July 6 and July 10, 2000, Mr. Armando Chavez representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 171) of the investigational drug, Prilosec (omeprazole magnesium) Tablets, performed for Astra Merck Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Chavez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[Handwritten Signature]

John R. Martin, M.D.  
Branch Chief  
Good Clinical Practices I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, Maryland 20855

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CFN: \_\_\_\_\_

Field Classification: NAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

- inadequate informed consent
- inadequate drug accountability
- failure to adhere to protocol
- inadequate records
- failure to report ADRS
- other

cc:

HFA-224  
HFD-180 Doc.Rm. NDA# 21-229  
HFD-180 Review Div.Dir. Talarico  
HFD-180 MO Avigan  
HFD-180 PM Walsh  
HFD-45 Reading File  
HFD-46 Chron File  
HFD-46 GCP/CIB File # 2958  
HFD-46 GCP/CIB Reviewer Malek  
HFD-46 GCP/CIB Br Chief Martin  
HFD-46 CSO Huff  
HFR-PA250 DIB Kozick  
HFR-PA2565 Bimo Monitor Koller  
HFR-PA2565 Field Investigator Chavez  
r/d: KM 6/25/01  
reviewed:JM:6/26/01  
f/t:jau:6/26/01  
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**Note to Rev. Div. M.O.**

The field investigator reviewed the records of 59 subjects out of 106 enrolled in the study. There was no deviation from Good Clinical Practice.  
The data appear acceptable to be used in support of the NDA.



NDA 21-229

Proctor & Gamble  
Attention: Linda C. Jones  
Senior Scientist, Regulatory Affairs  
Health Care Research Center  
8700 Mason-Montgomery Road  
Mason, OH 45040-9462

Dear Ms. Jones:

Please refer to the meeting between representatives of your firm, AstraZeneca LP, and FDA on January 30, 2001. The purpose of the meeting was to discuss the appropriate instructions for the OTC population with frequent heartburn for Prilosec 1 (omeprazole magnesium) Tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Maria Walsh

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** April 26, 2001  
**Time:** 2:30 p.m. - 3:30 p.m.  
**Location:** Parklawn Building, Conference Room "C"  
**Application:** IND 54,307  
Prilosec 1 (omeprazole magnesium) Tablets  
**Sponsor:** AstraZeneca, L.P./The Proctor and Gamble Co.  
**Type of Meeting:** Clinical Development  
**Meeting Chair:** Charles Ganley, M.D., Division Director, HFD-560  
**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### FDA Attendees:

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Lilia Talarico, M.D., Director  
Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader  
Mark Avigan, M.D., Medical Officer  
Marcelo Barreiro, M.D., Medical Officer  
Liang Zhou, Ph.D., Chemistry Team Leader  
Maria R. Walsh, M.S., Regulatory Project Manager

#### Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director  
Ling Chin, M.D., Medical Officer  
Mary S. Robinson, Interdisciplinary Scientist/Chemist  
Helen Cothran, Interdisciplinary Scientist/Chemist  
Dan Keravich, R.Ph., M.S., M.B.A., Regulatory Project Manager

### Sponsor Attendees:

#### AstraZeneca, L.P.

Mark Mallon, Vice President, Gastrointestinal Therapeutic Area  
Doug Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Ph.D., Executive Director, Regulatory

#### The Proctor and Gamble Co.

Tom Blinn, Vice President, Global Personal Health Care  
Robert Greene, VP Personal Health Care R&D  
Doug Ws.Bierer, Ph.D., Director, Regulatory  
Nora Zorich, M.D., Ph.D., Medical Director, Health Care  
Keith Triebwasser, Ph.D., Manager, External Relations, Regulatory Affairs

**Background:** NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, was determined to be not approvable on November 27, 2000 for three over-the-counter (OTC) indications: 1) relief of heartburn, indigestion, and sour stomach; 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages,

3) prevention of heartburn for 24 hours. The not approvable letter suggested that this drug product might be further developed for prevention of heartburn for 24 hours/treatment of frequent heartburn.

The Agency met with The Proctor and Gamble Company (agent) and AstraZeneca LP (sponsor) on January 30, 2001 to discuss the appropriate therapy for the target OTC population. The Agency recommended the sponsor submit a proposed actual use protocol and revised proposed labeling that addresses the possibility of chronic intermittent use and under treatment of consumers with gastroesophageal reflux disease (GERD).

The Proctor and Gamble Company submitted a pre-meeting briefing package, dated April 3, 2001, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for this meeting. The package includes proposed labeling, a proposed actual use protocol, and a list of questions.

**Meeting Objective:** To discuss whether the proposed labeling, in conjunction with the supporting program and data, adequately addresses the target population and use of Prilosec 1 in an OTC setting.

**Item 1: Proposed Labeling (Target population/Directions for use)**

The proposed labeling includes the following wording:

**Uses**

- for prevention of frequent heartburn
- intended for those who suffer heartburn two or more days per week

**Directions**

- \_\_\_\_\_ swallow 1 tablet with a glass of water in the morning
- \_\_\_\_\_ every day for up to 14 days

**Warnings**

Heartburn can be a sign of a more serious condition. \_\_\_\_\_, notify your doctor.

The Agency's introductory points may be summarized as follows:

"Prevention of frequent heartburn" is a new OTC indication. Consumers who are experiencing frequent heartburn may have gastroesophageal reflux disease (GERD), either symptomatic GERD or erosive esophagitis. Therefore, a dosing regimen of 20 mg every day for a set period of time is recommended.

The proposed direction, "... use every day for up to 14 days," will lead to PRN dosing. Data from clinical studies and published literature indicate that Prilosec should be used for a set period of time. Adequate data have not been provided to support the safety and efficacy of a PRN dosing regimen. The impact of PRN dosing on pathology and possible chronic intermittent use is unknown.

The proposed statement, \_\_\_\_\_, is arbitrary and does not adequately address the issue of possible chronic intermittent use. For example, the proposed labeling would allow consumers to \_\_\_\_\_

The proposed statement, \_\_\_\_\_, "notify your doctor," does not adequately define the time period nor does it specify whether the consumer should notify the doctor before or after taking Prilosec 1.

The sponsor's introductory points may be summarized as follows (presented as overhead slides):

Frequent heartburn (two or more episodes per week) is a specific, self-identifiable condition. Consumers with this condition can recognize the pattern and scope of their symptoms and identify the number of heartburn episodes they have each week.

Most consumers with frequent heartburn have uncomplicated frequent heartburn. Current OTC products do not adequately treat frequent heartburn.

Possible "at risk" conditions associated with frequent heartburn may not be self-identifiable, such as erosive esophagitis (prevalence: 2.4%), Barrett's esophagitis (incidence: 0.3%), or esophageal adenocarcinomas (deaths: 0.0002%). The potential that heartburn is a more serious medical condition is low.

acid secretion. The sponsor asked if the data supports labeling directions for the consumer to take one tablet every day for 14 days and if symptoms persist, to see a doctor. The Agency said there is some internal debate as to whether the dosing regimen should be 14 days or 28 days. The Nonprescription Drugs and Gastrointestinal Drugs Advisory Committees will make this determination.

The proposed PRN dosing regimen was discussed further. The sponsor said since the data demonstrate that Prilosec 1 is efficacious after a single dose, it should also be efficacious after a single dose every other day. The Agency had the following comments:

The data provided does not demonstrate that Prilosec 1 taken before a morning meal provides 24-hour prevention of heartburn.

Adequate data to support a PRN dosing regimen have not been provided.

The Nonprescription Drugs and Gastrointestinal Drugs Advisory Committees (joint meeting held on October 20, 2000) recommended a reasonable dosing regimen to ensure that those consumers with GERD who will use the product and not see a physician are adequately treated.

---

To support a PRN dosing regimen, the actual use study should demonstrate that consumers will stop using the product and see a physician when appropriate. In addition, a rationale for the proposed \_\_\_\_\_ should also be provided.

Regarding the Agency's recommendations, the sponsor had the following comments:

Compliance with a 14- or 28-day dosing regimen would be difficult to accomplish in an actual use study.

Effectiveness in the OTC setting is based on managing symptoms (i.e. frequent heartburn) not underlying pathology (i.e. erosive esophagitis, Barrett's esophagus). It is irrelevant to assess underlying pathology in clinical studies for PRN dosing when the desired outcome in any case is for consumers to stop using the product and see a physician when symptoms are unresolved.

The sponsor agreed that chronic intermittent use is a safety concern and the actual use study should demonstrate that consumers will stop using the product and see a physician

when appropriate.

The Agency provided the following additional comments regarding the labeling:

Distinction from the acid reducers is desirable but \_\_\_\_\_ as the purpose of the drug product may not be acceptable. Further consideration is needed.

Under the "Do not use" section, \_\_\_\_\_  
\_\_\_\_\_

Under the "Ask a doctor or pharmacist before use if you are taking" section, brand names are not permitted in the Drug Facts box.

**Item 2: Proposed Actual Use Protocol**

The proposed actual use protocol was not discussed in detail. The Agency will address the sponsor's written questions and provide comments on the proposed actual use protocol in a follow-up letter to issue in approximately one month from the date of this meeting.

**Conclusion:** The Agency will provide written comments on the proposed labeling and the proposed actual use protocol in a follow-up letter to issue in approximately one month from the date of this meeting.

Minutes Preparer: \_\_\_\_\_

Chair Concurrence: \_\_\_\_\_

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Meeting Minutes  
Page 7

Drafted: M. Walsh 5/15/01  
Initialed by: M. Avigan 5/16/01  
          H. Gallo-Torres 5/16/01  
          L. Talarico 5/16/01  
          C. Ganley 5/23/01

Final: M. Walsh 5/23/01

Filename: C:\mydocuments\154307.April-2001.minutes.doc

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/s/

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Charles Ganley  
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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** January 30, 2001  
**Time:** 9:30 a.m. - 11:00 a.m.  
**Location:** Parklawn Building, Conference Room "K"  
**Application:** NDA 21-229  
Prilosec 1 (omeprazole magnesium) Tablets  
**Sponsor:** AstraZeneca, L.P./The Procter and Gamble Co.  
**Type of Meeting:** Clinical Development  
**Meeting Chair:** Charles Ganley, M.D., Division Director  
**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager

### FDA Attendees:

#### Office of Drug Evaluation III (HFD-103)

Victor F. C. Raczkowski, M.D., M.S., Deputy Director

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Lilia Talarico, M.D., Director

Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader

Mark Avigan, M.D., Medical Officer

Scheldon Kress, M.D., Medical Officer

Maria R. Walsh, M.S., Regulatory Project Manager

#### Division of Pharmacological Evaluation II (HFD-870)

Suresh Doddapaneni, Ph.D., Team Leader

Suliman Al-Fayoumi, Ph.D., Reviewer

#### Division of Biometrics II (HFD-715)

Thomas Permutt, Ph.D., Team Leader

Wen-Jen Chen, Ph.D., Statistical Reviewer

#### Office of Drug Evaluation V (HFD-105)

Robert DeLap, M.D., Ph.D., Director

#### Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director

Ling Chin, M.D., Medical Officer

Mary S. Robinson, Interdisciplinary Scientist/Chemist

Helen Cothran, Interdisciplinary Scientist/Chemist

Dan Keravich, R.Ph., M.S., M.B.A., Regulatory Project Manager

**Sponsor Attendees:**

AstraZeneca, L.P.

Doug Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area

Gary Horowitz, Ph.D., Executive Director, Regulatory

[ \_\_\_\_\_ ] / Consultant

George Kummeth, Associate Director, Regulatory

Tommy Andersson, Ph.D., Pharmacokineticist

The Proctor and Gamble Co.

Doug Ws.Bierer, Ph.D., Director, Regulatory

Lisa D. Allgood, Associate Director, Research & Development

Nora Zorich, M.D., Ph.D., Medical Director, Health Care

William Kozarek, Ph.D., Principal Scientist, Regulatory Affairs

Linda C. Jones, Senior Scientist, Regulatory Affairs

Robert Greene, VP Personal Health Care R&D

[ \_\_\_\_\_ ] Consultant

**Background:** NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, was determined to be not approvable on November 27, 2000 for three over-the-counter (OTC) indications: 1) relief of heartburn, indigestion, and sour stomach; 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise; and 3) prevention of heartburn for 24 hours. The not approvable letter suggested that this drug product may be further developed for prevention of heartburn for 24 hours/treatment of frequent heartburn.

The Proctor and Gamble Company (agent for the sponsor, AstraZeneca, LP) submitted a pre-meeting briefing package, dated January 12, 2001, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for this meeting. The package included a list of questions/issues reproduced below.

**Meeting Objective:** To discuss the appropriate instructions for the OTC population with frequent heartburn.

**Issue 1:** Appropriate Use Directions for Ome-Mg in the Target Population  
... swallow 1 tablet with a glass of water,

We are in agreement with the Agency that the most appropriate subject population for the OTC use of Ome-Mg is in those consumers who have heartburn more than once a week. We do, however, disagree with the Agency's guidance for use which would require consumers to take Ome-Mg for 28 continuous days. Our data support that, whether the OTC user has heartburn more

than once per week or daily, PRN dosing is the most appropriate pattern of therapy for OTC use.

We want to dedicate a significant portion of time to discuss the above directions for use and agree upon a position that will provide the consumer the appropriate dosing of this product in an OTC setting.

**Issue 2:      Duration of Maximum OTC Use**  
                  ... swallow 1 tablet with a glass of water,  
                  14 days

Consumers will be instructed to see a doctor when they find they need to use the product for longer than 14 days in a row. Fourteen days of "as needed" use is a sufficient limit for OTC use without physician/medical professional guidance to allow consumers to establish a pattern of use that signals a need to seek physician/medical professional guidance.

Based on our benefit-to-risk analysis, does the Agency agree with this position?

***Agency Response to Items 1 and 2:***

The following responses were provided to the sponsor in writing at the beginning of the meeting with the stipulation that they are subject to revision based upon further discussion at this meeting.

- The Agency does not agree with the sponsor's definition of frequent heartburn (i.e. more than once a week). The Agency believes that consumers who are experiencing frequent heartburn have gastroesophageal reflux disease (GERD), either symptomatic GERD or erosive esophagitis.
- The sponsor should define the target population.
- The sponsor should demonstrate that consumers know the difference between prevention of heartburn and treatment of heartburn and will use the product for prevention of heartburn only.
- The proposed PRN dosing implies treatment of heartburn. However, the pharmacokinetics/pharmacodynamics/clinical properties of the drug are not suitable for the proposed "as needed" dosing for reasons that include lack of efficacy for the treatment of acute heartburn. In addition, this approach will under treat consumers with GERD.
- The proposed instructions for duration of maximum use (i.e. 14 days) do not address the possibility of chronic use. In addition, the impracticability of treating GERD (whether symptomatic GERD or erosive esophagitis) short-term needs to be considered. Furthermore, the issue of when the consumer should seek medical assistance

should be carefully addressed.

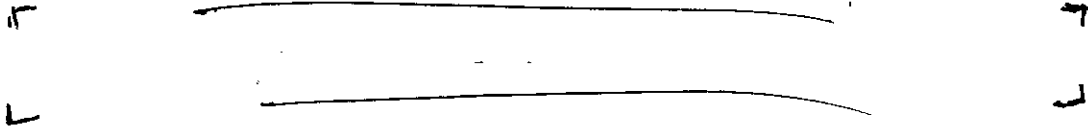
**Discussion:**

A discussion ensued about the following issues: target population and appropriate dosing.

The sponsor's major points may be summarized as follows:

- The targeted OTC population consists of consumers with frequent heartburn (more than one episode per week). This population may include some consumers with undiagnosed gastroesophageal reflux disease (GERD) or erosive esophagitis. (It should be noted that Dr. Robinson agreed that all individuals with frequent heartburn have GERD, but most consumers in the OTC setting have mild disease, either symptomatic only or small esophageal erosions).
- Because the targeted population has a spectrum of treatment needs, "as needed" or PRN dosing ( 14 days . ) is more appropriate than a prescribed course of therapy (e.g. every day for 28 days). Consumers tend to use a PRN dosing regimen even in a prescription course of therapy for GERD under a physician's care.
- For those OTC consumers with undiagnosed GERD or erosive esophagitis, lack of treatment response or return of symptoms following ( 14 days . ) should signal the consumer to follow the labeled directions and seek medical care. A short delay in obtaining medical care (2 weeks) in these consumers is not a significant safety concern.

The Agency's major points may be summarized as follows:

- The Agency reiterated its belief that many consumers who are experiencing frequent heartburn may have GERD, and some may have erosive esophagitis.
- 
- The proposed duration of maximum use ( 14 days . ) does not address the under treatment of GERD nor the possibility of long-term intermittent use ( ). This would further delay diagnosis and adequate medical treatment for consumers with undiagnosed GERD and more importantly, for consumers with undiagnosed Barrett's esophagus or cancer. Also, the proposed label does not ensure that consumers will only use the product for prevention of heartburn and not for treatment of acute symptomatic heartburn.

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The Agency advised the sponsor to carefully define the target OTC population, demonstrate that the majority of consumers participating in the actual use study have mild disease and revise the label to ensure that those consumers with more serious disease seek medical care. The sponsor requested guidance from the Agency in designing a study that would monitor physician involvement.

The sponsor agreed that the proposed labeling should be revised to address the possibility of chronic intermittent use. There was some discussion about how consumers used the drug in the completed actual use studies and possible options for revising the labeling.

**Conclusion:** Based on the above discussion, the sponsor will submit a revised protocol design and revised proposed label for review by the Agency. The proposed label should address the possibility of chronic intermittent use and under treatment of consumers with GERD. Further discussion between the sponsor and the Agency is needed.

**Issue 3: Drug Interactions**

We are seeking guidance on whether we need to include drug interactions on our label and, if so, the Agency's rationale.

**Agency Response:**

This agenda item was not discussed. The following Agency responses were provided to the sponsor in writing at the beginning of the meeting.

The following drug interactions should be included on the label:

- Ketoconazole \_\_\_\_\_
- \_\_\_\_\_
- [ \_\_\_\_\_ ]
- [ \_\_\_\_\_ ]

Phenytoin and warfarin [ \_\_\_\_\_ ]

**Issue 4: Use Study Design**

We are proposing an Actual Use Study as outlined in this briefing document based on an "as needed" dosing up to 14 days. We have included a study outline and flow diagram for enrollment/disposition of study participants. Based on the Agency feedback on our NDA, we have designed this study with minimum intervention.

We welcome your comments on the design elements of self-selection, compliance measurements, duration of the study, reasonable time in which to seek physician/medical professional guidance and who should seek physician guidance.

***Agency Response:***

This agenda item was not discussed. The Agency will provide specific recommendations once the Agency can agree with the sponsor on the Use and Directions for the drug product. Any study should take into account any ancillary measures to insure compliance with the labeled instructions.

Minutes Preparer: \_\_\_\_\_

Chair Concurrence: \_\_\_\_\_

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Meeting Minutes  
Page 7

Drafted: M.Walsh 3/28/01

Initialed by: H.Gallo-Torres 3/29/01

L.Talarico 4/2/01

V.Raczkowski – No comments received

R. DeLap 4/4/01

C. Ganley 4/9/01

Final: M.Walsh 5/7/01

Filename: C:\mydocuments\21229.January-2001.meeting.minutes.doc

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Charles Ganley

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## MEMORANDUM OF T-CON MEETING MINUTES

**Meeting Date:** January 22, 2001  
**Time:** 9:30 a.m. - 10:00 a.m.  
**Location:** Parklawn & Corporate Buildings

**Application:** NDA 21-229  
Prilosec 1 (omeprazole magnesium) Tablets

**Sponsor:** The Proctor and Gamble Co & Astra Zeneca, L.P.

**Type of Meeting:** T-Con: Clinical Development Status Update Meeting

**Meeting Chair:** Victor F. C. Raczowski, Deputy Director, ODE III,  
HFD-103 and Acting Director, HFD-180

**Meeting Recorder:** Dan Keravich, Regulatory Project Manager

### **FDA Attendees:**

Office of Drug Evaluation III (HFD-103)  
Florence Houn, Director

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)  
Victor F. C. Raczowski, Acting Director  
Joyce Korvick, Deputy Director  
Maria R. Walsh, Regulatory Project Manager

Division of Over-The-Counter Drug Products (HFD-560)  
Charles Ganley, Director  
Dan Keravich, Regulatory Project Manager

### **Sponsor Attendees:**

Astra Zeneca  
Lisa Pastorius, Project Leader  
Mark Mallon, Vice President, Gastrointestinal Therapeutic Area  
Doug Levine, Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Executive Director, Regulatory  
Miles McKiernan, Product Manager, Prilosec

The Proctor and Gamble Co  
Doug Bierer, Director, Regulatory  
Robert Greene, VP, Worldwide OTC Healthcare R&D  
Tom Blinn, VP, General Manager, Worldwide OTC Healthcare  
Keith Triebwasser, Sr. Director  
Joe Arcuri, North American General Manager

### **Background**

The Agency was asked to provide guidance and feedback in a correspondence dated October 5, 2001 concerning issues related to the duration of therapy and type of claim for Prilosec in an OTC environment.

**Status Update**

The Agency informed the sponsors that the Agency has held a series of internal discussions as well as meetings with three outside consultants who were members of the respective advisory committees to help the Agency address these issues. In summary:

- A variety of different opinions were received on these issues.
- Depending on the data, duration of therapy of 2 or 4 weeks may be acceptable.
- Ultimately, these issues are review issues.

The Agency will be interested in the response rates for the relief of frequent heartburn. Other major issues in the resubmission should address the following points:

1. Compliance rates with the proposed label.
2. What percentages of consumers who relapse do go back and see their physician, and what course of action was undertaken.

The Agency reminded the sponsor that a high threshold for success was needed and other issues including labeling comprehension would be important in the resubmission. The Agency stated that these were not all-inclusive issues.

**Sponsor Response:**

The sponsor provided a brief summary of the information they plan to include in their re-submission.

The Agency reminded the sponsor that another Joint Advisory Committee review might be necessary if the Agency believes relevant.

**Action Items**

The sponsor plans to re-submit their application in mid-February.

The feedback meeting ended amiably.

Meeting Minutes Prepared By: Dan Keravich  
Meeting Chair Concurrence By: Victor F. C. Raczowski

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/s/

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Daniel Keravich:  
3/5/02 02:15:54 PM  
CSO

Victor Raczkowski  
3/5/02 06:31:06 PM  
MEDICAL OFFICER

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## MEMORANDUM OF TELECONFERENCE MEETING

**Meeting Date:** December 21, 2000

**Time :** 11:30AM

**Location:** S200A, 9201 Corporate Blvd  
Rockville, MD

**Application:** NDA 21-229 Prilosec

**Type of Meeting:** Sponsor feedback concerning the Not Approved Letter

**Meeting Chair:** Charles Ganley, M.D., Division Director, HFD-560

**Meeting Recorder:** Daniel P. Keravich, R.Ph, M.S., M.B.A.

### TELECONFERENCE PARTICIPANTS

#### Procter & Gamble

Robert Greene, VP Personal Health Care R&D  
Douglas Bierer, Ph.D., Director, Regulatory Affairs  
Bill Kozarek, Ph.D., Principal Scientist, Regulatory Affairs  
John McRorie, Ph.D., Clinical Senior Scientist  
Linda Jones, Regulatory Affairs  
Nora Zurich, Director Medical Affairs

#### Astra Zeneca

Doug Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Ph.D., Executive Director, Regulatory  
J Consultant  
George Kummeth, Associate Director, Regulatory  
Lisa Pastorius, Project Team Leader

#### Agency Participants

Robert DeLap, Ph.D., M.D., Director, ODE V, HFD-105  
Lilia Talarico, M.D., Division Director, HFD-180  
Mark Avigan, M.D., Medical Officer, HFD-180  
Hugo Gallo-Torres, M.D., Team Leader, HFD-180  
Charles Ganley, M.D., Division Director, HFD-560  
Ling Chin, M.D., Medical Officer, HFD-560  
Larry Goldkind, M.D., Team Leader, HFD-550  
Dan Keravich, R.Ph., M.S., M.B.A., Regulatory Project Manager, HFD-560

**Objectives:**

To provide sponsors with feedback concerning issues raised in the not approval letter dated November 27, 2000. The sponsor has provided 6 specific questions or issues raised in the letter that were sent to the Agency on December 11, 2000. The questions and responses are as follows:

**Issues:**

- 1A. You have not provided sufficient evidence to establish efficacy of single 10 mg or 20 mg doses of OME-Mg for relief of heartburn symptoms (studies 1997092 and 1997095)...**

We agree that studies 1997092 and 1997095 did not establish efficacy after the first dose of OME-Mg for the relief of heartburn. Given this, and in light of the FDA concern expressed in 1E of your letter that both the actual use and label comprehension trials failed to demonstrate that consumers understood how and when to use OME in comparison to currently available OTC heartburn products that are marketed for relief .... of heartburn, please note that our proposed label will focus exclusively on prevention indications for OME-Mg. We believe this differentiates OME-Mg from currently OTC heartburn products marketed for relief. As such, this should make the label even more easily understood. We'd appreciate the Agency's comments on this.

***Agency's Comments***

- Sponsor needs to provide self-selection / actual use studies that demonstrate that the consumer understands how to self select and use the product for prevention only.
- Sponsor is reminded to minimize the exclusion criteria for these studies.

- 2. Issue: 1A. You have not provided sufficient evidence to establish efficacy of single 10 mg or 20 mg doses of OME-Mg for .....prevention of meal-induced heartburn (studies 1998005 and 1998006).**

Please note that study 1998006 demonstrated efficacy for the primary variable when dosed one hour prior to eating while study 1998005 did not. However, all other variables in both studies showed a consistent and statistically significant therapeutic gain associated with the 20 mg dose. Furthermore, the pooled analysis showed statistical significance for all variables for both doses except the use of back up medication for the 10 mg dose.

Also, with regard to prevention, we would point out that Studies 171 and 183 supported effectiveness for the prevention of heartburn when dosed in the morning, and, importantly, efficacy was demonstrated after the first dose in these trials.

We are seeking FDA's input on the utility of these 4 studies in supporting and defining a dosing time frame for 24 hour prevention of heartburn when heartburn is expected. We feel that the 4 studies adequately support and delineate a use instruction for prevention such as:

For 24 hour prevention of heartburn:

swallow a single tablet with a glass of water either:

- in the morning (study 171 and 183, specifically first dose data)
- or at least one hour prior to eating foods or drinking beverages you expect may cause heartburn. (study 1998005 and 1998006)

Does the Agency agree that the data from these studies support a prevention claim in this context?

***Agency's Response***

No, this is a subgroup of the frequent heartburn population who should probably not be taking this product on an intermittent basis. We do not believe that this product's clinical and pharmacodynamic profile is suitable for prevention of meal induced heartburn. We further address this issue in the response for the next question.

3. **Issue: 1A. The data presented for prevention of heartburn for 24 hours (studies 171 and 183) do support the efficacy of either 10 mg or 20 mg per day dosing for up to 10 days in the treatment of individuals with chronic heartburn.**

Please note that we did not intend to develop OME-Mg for the treatment of symptomatic GERD, although we acknowledge that some patients with GERD were likely studied in 171 and 183 given our screening protocol did not include endoscopic study subjects. We believe that GERD should be diagnosed and treated by a physician. Thus, our efforts are in the direction of developing adequate labeling that will direct the patient with GERD to seek medical advice at the appropriate point in time.

We would rely on the data in 171 and 183 to support efficacy and safety for the prevention of heartburn in consumers who have frequent heartburn to show that these consumers can take OME-Mg as needed, as frequently as everyday to prevent their heartburn. However, if a consumer needs to take this product everyday for more than a 2 week period, we feel that he/she should seek the advice of a health care professional. Thus, studies 171 and 183 can be relied upon to support the safety for the 2 week interval.

***Agency's Comments***

- The Agency believes that a frequent heartburn indication will include individuals with GERD.
- The agency has concerns that many people in these studies (and many who would take an OTC product) actually have GERD. Intermittent use may not be adequate treatment for frequent heartburn and could lead to chronic dosing without the intervention of a physician.

- If there is a differentiation to be made, sponsor is requested to differentiate frequent and or chronic heartburn from GERD with symptomatic /diagnostic criteria. Sponsor is requested to specify the inclusion and exclusion criteria that will define the population of interest.
- Any attempt to market to a population of occasional frequent heartburn sufferers is likely to include consumers who frequently suffer from heartburn all of the time. The sponsor would have to demonstrate that they can create a label that would allow a population of occasional frequent heartburn sufferers to correctly self-select (in a self-selection/actual use trial) without also attracting consumers who suffer from frequent heartburn all of the time.

**Issue: 1B While periods of self-treatment may provide an acceptable standard of care for a subset of individuals with GERD, you need to establish that consumers understand when to contact their physicians prior to initiating therapy and also that consumers understand when to follow-up with their physicians after initiating therapy.”**

The current labeling for OTC products instructs the individual to consult their doctor *prior* to use if they have difficulty swallowing, or if they are taking medications listed on the label, or if they are pregnant or nursing. We have proposed adding two additional alarm symptoms to the label which may be indicative of a more serious condition for which we will instruct the consumer to seek a doctor's advice prior to use. The two additional warnings under consideration are sudden weight loss or a wheezing, \_\_\_\_\_

In addition, individuals are instructed to seek doctor's care *after* trying the medication if it is ineffective or if they find they need to use the drug for 14 days (as is the case with acid reducers).

Since these label instructions are related to a potential underlying condition or disease and to the efficacy of the various treatments in reducing the acid exposure of the esophagus, it would seem that warnings to consumers should be consistent among all the OTC heartburn treatments.

Does the Agency agree that such “class” labeling is appropriate in the OTC heartburn setting?

#### ***Agency's Response***

- The Agency does not believe that the discussion of “class labeling” is a relevant discussion point at this time. They can choose to include warnings that they believe to be appropriate for the safe use of the product. The appropriateness of the warning should be supported by the sponsor.

5. **Issue: 1D. Similarly, use of a 20 mg daily dose for four weeks by consumers with GERD and/or erosive esophagitis may be an adequate regimen for some but an inadequate regimen for others."**

Please note that we did not intend to develop OME-Mg for the self-diagnosed treatment of GERD, nor do we believe that a 4week self-treatment regimen is appropriate in the OTC setting. We believe that GERD should be diagnosed and treated by a physician. We are now suggesting a prevention paradigm that may include treatment up to 14 days. It is in this overall label context (prevention indication, warnings, usage) that 20mg appears to be the preferred OTC dose; we are interested in obtaining the Agency's point of view on dose.

*Agency's Comments*

The dose and duration of therapy should be appropriate for the individuals who will use the product OTC. The Agency's expectation is that product labeling should generally provide for adequate treatment for the consumer's condition, and should not recommend treatment that may be insufficient for many of the consumers who will actually use the product OTC. The Agency's preference is to provide maximum benefit to consumers.

6. **Issue: 2. Prilosec has a number of reported drug-drug interactions. Prilosec is metabolized by the cytochrome P450 enzymes. In some individuals, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, warfarin,**

These interactions are based on data from studies with 40 mg of omeprazole. We do not expect, nor have we observed, clinically relevant metabolic drug-drug interactions during concomitant treatment with daily dosing of 10 or 20 mg omeprazole.

Has the Agency developed a position related to the OTC labeling for the drugs cited above?

*Agency's Response*

- An adequate labeling and the actual use studies can potentially address these issues. The agency can better address this issue in the next face to face meeting in January.
- If the sponsor's intent here is to determine whether they should include the drugs listed above in their labeling so that they could study it in the self-selection/actual use study, they were encouraged to do so.

Minutes Submitted By: Dan Keravich\_\_\_\_\_

Chair Concurrence By: Charles Ganley\_\_\_\_\_

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/s/

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Charles Ganley

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** December 12, 2002  
**Time:** 12:15 p.m.- 1:00 p.m.  
**Location:** Parklawn Building, Conference Room "B"  
**Subject:** IND 54,307  
Omeprazole Magnesium Delayed-Release Tablets  
**Meeting Chair:** Hugo Gallo-Torres, M.D., GI Medical Team Leader, HFD-180  
**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### **FDA Attendees:**

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert Justice, M.D., Director  
Hugo Gallo-Torres, M.D., GI Medical Team Leader  
Liang Zhou, Ph.D., Chemistry Team Leader  
Arthur Shaw, Ph.D., Chemistry Reviewer  
Maria R. Walsh, M.S., Regulatory Project Manager  
Susan Daugherty, Regulatory Project Manager

#### Division of Over-The-Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director  
Daiva Shetty, M.D., Medical Officer  
Helen Cothran, Interdisciplinary Scientist/Chemist  
Mary S. Robinson, Interdisciplinary Scientist/Chemist  
Walter Ellenberg, Regulatory Project Manager

### **Sponsor Attendees:**

#### AstraZeneca, LP

Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs

#### The Proctor and Gamble Company

Thomas C. Blinn, Vice President, Global Personal health Care  
Robert A. Greene, Vice President, product Development  
Joseph A. Arcuri, General Manager, Personal Health Care NA  
Keith C. Triebwasser, Ph.D., Senior Director, Regulatory Affairs  
Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**Background:** NDA 21-229, Omeprazole Magnesium Delayed-Release Tablets, was resubmitted on February 12, 2002 (in response to a not approvable letter, dated November 27, 2000) for the following proposed indication: prevention of the symptoms of frequent heartburn for 24 hours. An approvable letter was issued on August 8, 2002. A teleconference was held between FDA and representatives of AstraZeneca (sponsor) and The Proctor and Gamble Co. (sponsor's agent) on August 8, 2002 to discuss the main points of the action letter. An end-of-review meeting was held on October 9, 2002 between FDA and representatives of the sponsor and agent to discuss the action letter in more detail. During that meeting, Proctor and Gamble's intention \_\_\_\_\_ was discussed briefly. FDA advised the sponsor to request another meeting to discuss this issue in more detail.

Proctor and Gamble submitted a meeting request, dated October 11, 2002, and a pre-meeting briefing package, dated November 20, 2002, to the Division of Gastrointestinal and Coagulation Drug Products in preparation for today's meeting. The package includes Proctor and Gamble's proposals for commercial package sizes and a sampling program for health care providers and consumers with frequent heartburn.

**Meeting Objective:** To discuss Proctor and Gamble's proposals for marketing \_\_\_\_\_ commercial package sizes and distributing \_\_\_\_\_ packages (starter kits) to health care providers (physicians and pharmacists) and consumers with frequent heartburn.

**Agenda Item 1: Commercial Package Sizes**

FDA noted that the current draft labeling for Prilosec OTC (omeprazole magnesium) Delayed-Release Tablets recommends a 14-day course for the treatment of frequent heartburn. FDA asked Proctor and Gamble to provide a rationale for marketing larger than 14-count package sizes and to explain how this approach will not lead to chronic long-term use.

Proctor and Gamble made the following points:

- The results of the label comprehension study 22103 (provided in tabular format) demonstrate that consumers understand that the course of treatment is 14 days, that another 14-day course may not be started for 4 months, and to ask a doctor if heartburn continues after 14 days.
- Two or three individual 14-count cartons packaged together in a larger multi-course carton will not lead consumers to use the product any differently than if they buy two or three individual 14-count packages at the same time. The multi-course carton might reinforce the concept that each component is a separate 14-day course of treatment.



**FDA comments:**

- **The starter kit package should clearly explain that appropriate use of Prilosec OTC requires 14 consecutive days of treatment and is not intended for intermittent use. Each 2-count sample card should be dispensed with the approved package insert.**
- **The title "Drug Facts" on the sample card should be deleted. Follow Labeling Requirements for OTC Drugs as specified in 21 CFR 201.66.**
- **FDA will consider whether the package insert should be attached to the sample card.**
- **The survey sample to be used for the identification of consumers with frequent heartburn should be included in the NDA resubmission for review.**
- **The 2-count sampling program proposal should be included in the NDA resubmission for final review.**

Minutes Preparer: Maria R. Walsh, M.S.

Chair Concurrence: Hugo Gallo-Torres, M.D.

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Maria Walsh  
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## MEMORANDUM OF TELECON

DATE: November 20, 2000

APPLICATION NUMBER: NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets

BETWEEN:

The Proctor and Gamble Company

Robert Greene, VP Personal Health Care R&D  
Nora Zorich, M.D., Ph.D., Director, New Drug Development  
Keith Triebwasser, Ph.D., Director, Regulatory Affairs  
Douglas Bierer, Ph.D., Director, Regulatory Affairs  
Linda Jones, Regulatory Affairs

AstraZeneca LP

Ron Krall, M.D., Sr. VP US Drug Development  
Doug Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area  
Gary Horowitz, Ph.D., Executive Director, Regulatory  
George Kummeth, Associate Director, Regulatory

AND

FDA

Robert DeLap, M.D., Director  
Office of Drug Evaluation V, HFD-105

Victor Raczkowski, M.D., Deputy Director  
Office of Drug Evaluation III, HFD-103

Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Status of review/action letter

BACKGROUND: AstraZeneca LP (sponsor) together with The Proctor and Gamble Company (agent) submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, on January 27, 2000 for the following over-the-counter (OTC) indications:

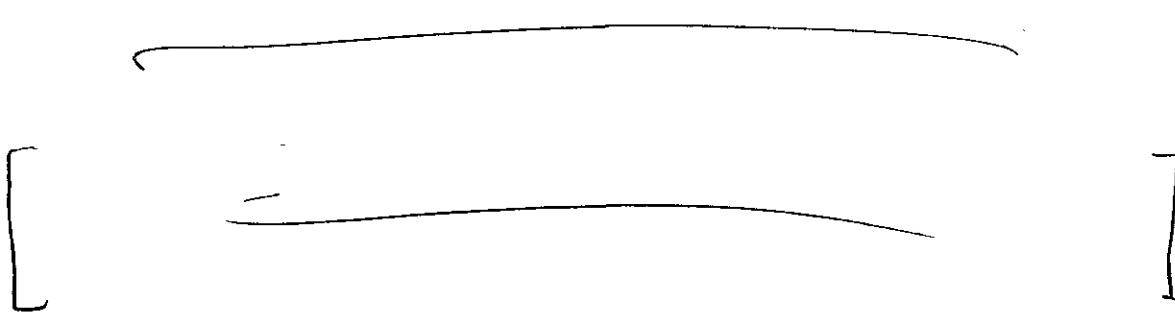
- Relief of heartburn, acid indigestion, and sour stomach.
- Prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages,
- Prevention of heartburn for 24 hours.

This application was discussed at the Joint Non-Prescription Drugs/Gastrointestinal Drugs Advisory Committee Meeting on October 20, 2000. The primary action due date is November 27, 2000.

**DISCUSSION:** The Agency informed the sponsor/agent that the review of this application is near completion and a not approvable action letter is being drafted. The data to support the treatment of heartburn symptoms with a single dose, or to prevent heartburn with a single dose taken shortly before a meal or other heartburn-inducing event, is not deemed sufficient. The data in the application do provide support for the use of repeated daily doses of 10 mg or 20 mg Prilosec 1 for the "prevention of heartburn for 24 hours" (or treatment of frequent heartburn). Regarding this indication, however, the Agency has unresolved concerns regarding identification of the appropriate dose and duration of therapy, and the ability of the consumer to self-select and to use the drug safely and effectively in the OTC setting. The Agency explained that a not approvable action would be taken rather than an approvable action because the number and nature of the unresolved issues are substantial, and it is not certain that they can all be adequately addressed.

The sponsor asked the Agency to further clarify the concern regarding the appropriate dose and duration of therapy. The Agency said one of the concerns is the possibility of undertreatment for some consumers, and the potential risks associated with undertreatment. The population of consumers who would use Prilosec 1 daily for "frequent heartburn" would likely encompass many individuals with gastroesophageal reflux disease (GERD), who may need a higher dose and/or longer duration of therapy than currently proposed, and at least some of whom should consult a physician. It is important to establish that the product labeling provides for a dose and duration of therapy that will represent adequate treatment for the consumers who use the product, as well as providing clear guidance on self-selection and when to see a health care professional.

When asked if the Agency's concerns can be addressed by a new actual use study only, the Agency staff said it is not clear at this time whether additional clinical studies are needed. At least some of the additional clinical data that may be needed may already be available in the clinical trials database for Prilosec. New label comprehension and actual use studies will be required. The product label should adequately address consumer self-selection, warnings, and when to see a health care professional (e.g. some consumers should consult a physician before taking the drug, and some consumers should consult a physician after taking the drug for a period of time). In essence, the label should assist the consumer in using the drug wisely and obtaining maximum benefit.



The sponsor asked if the Agency considered "the prevention of heartburn for 24 hours" and the sponsor's recently proposed indication for "the treatment of frequent heartburn" the same indication. The Agency said they can be considered the same indication but suggested that consumers may more readily understand "treatment of frequent heartburn".

The sponsor asked if the Agency has any other outstanding concerns related to the drug product. The Agency said other safety concerns that remain under consideration include: 1) use of the drug in special populations such as children and pregnant women; 2) effects of hypergastrinemia with longer-term use; 3) potential genotoxic effects; and 4) drug-drug interactions. The Agency added that some safety issues are of more concern if consumers take the drug long-term without consulting a physician and of less concern if consumers consult a physician before/during such use.

The Agency said that the Joint Non-Prescription Drugs and Gastrointestinal Drugs Advisory Committee would likely be asked its for advice again if the sponsor seeks approval of the drug in the future. However, some safety issues may be better discussed at an Advisory Committee considering all proton pump inhibitors, and issues related to the appropriateness of GERD as an OTC indication may also be discussed further at an Advisory Committee meeting.

The Agency said the proposed proprietary name is not appropriate because use of the number suffix "1" has no obvious relevance to the product dose or use and may be misleading. The sponsor explained that the number suffix was added to the product name to ensure compliance with the recommended once daily dose. The Agency said since other dosing compliance issues exist, such as the possibility of repeated courses or intermittent use, the sponsor should consider packaging alternatives that encourage compliance with the dosing regimen(s) that will be recommended in final labeling.

The Agency said the above discussion included essentially all of the issues to be detailed in the action letter. Issuance of a not approvable letter would provide the sponsor with a complete list of all "approvability" deficiencies following review of the current application.

The sponsor said it plans to submit a meeting request within the next few days to discuss how to address the deficiencies. The Agency said the official meeting request should be submitted after receipt of the action letter, but potential meeting dates may be considered now. The meeting request should be submitted to NDA 21-229. Any subsequent protocols should be submitted to IND 54,307.

No further issues for discussion were identified and the call was then concluded.

APPEARS THIS WAY  
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Robert DeLap, M.D.  
Director, ODE V

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Victor Raczkowski, M.D.  
Deputy Director, ODE III

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Maria Walsh  
12/12/00 10:39:40 AM  
CSO

Robert DeLap  
12/13/00 04:13:07 PM  
MEDICAL OFFICER

Victor Raczkowski  
12/13/00 04:56:11 PM  
MEDICAL OFFICER

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ON ORIGINAL

Memo/Comments on the package for NDA 21-229 prilosec 1 (omeprazole magnesium) tablets

AJacobs 11/14/00 N21229.doc

I. Comments on the pharm/tox review and the team leader memorandum of 9/13/00

A. If adequate AUC data are available for rats, these data should be used in calculating multiples of the human exposure in the pharm/tox portion of the proposed labeling.  $Mg/m^2$  conversion of the doses corrects exposure for body surface area but does not adjust for bioavailability. The multiples of human exposure based on body surface area conversions will result in a multiple of human exposure about 7 times smaller than mg/kg comparisons. Based on 10-20-fold lower bioavailability in rats compared to humans, AUC values may be 10-20 times lower than the body surface area comparisons (or 70-140 times lower than mg/kg comparisons). This means that the studies described in the label were not conducted at enormous multiples of the human systemic exposure.

II. Comments on the memorandum of the medical team leader of 10/23/00

A. Page 14 second half of the page

1. \_\_\_\_\_  
\_\_\_\_\_ The genotoxicity data are rather clear.

2. The statement after the first dash needs correcting: Studies were not conducted with human bone marrow cells. Delete, \_\_\_\_\_

3. I suggest deleting the material following the third dash. Perhaps just say that genotoxicity was mentioned.

- a. A negative result in an Ames assay does not counterbalance the clastogenicity results
- b. The purported result with azoxymethane (Penman et al. 1993) does not counterbalance the carcinoid results in the rats. That azoxymethane study does not appear to have been confirmed. On the contrary, in subsequent studies either no effect on azoxymethane-induced colon cancer was seen (Pinson et al., 1995) or omeprazole increased the average number and size of aberrant crypt foci in rats receiving azoxymethane (Martelli et al., 1998). Even if the study had been confirmed, the results are irrelevant to the carcinogenic effect of omeprazole on the stomach. Omeprazole could prevent formation of the carcinogenic metabolite of azoxymethane or react with the metabolite directly. A mechanism that would be relevant to humans is not apparent.

B. Top of page 15

Without very close follow-up, the risk of malignancy may never be detected. See also comments under IID. below.

C. First bullet on page 15

Nonclinical studies suggested postimplantation effects and postnatal effects. Embrolethality is extremely difficult to detect in humans, and postnatal behavioral effects may not be apparent until several years after birth. It's not clear how studies in humans will discern the presence or absence of such effects.

D. Second bullet on page 15

Surveillance for ECL carcinoids does not take into account the carcinogenic effects seen in the recently submitted 1-yr study in rats in which sites other than the stomach were affected (see pharm/tox supervisor memo). The risk for humans may extend beyond the consequence of drug-induced hypergastrinemia.

III.

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Abby Jacobs  
11/15/00 07:17:06 AM  
PHARMACOLOGIST

APPEARS THIS WAY  
ON ORIGINAL

D. Kerntsch

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

Date: November 13, 2000

From: Linda M. Katz, M.D., M.P.H. [ B/ ]  
Deputy Director, Division of Over the Counter Drug Products

Through: Charles Ganley, M.D. [ B/ ]  
Director, Division of Over the Counter Drug Products

To: Robert Delap, M.D.  
Director, Office of Drug Evaluation V

Florence Houn, M.D.  
Director, Office of Drug Evaluation III

Subject: NDA: 21-229: Prilosec 1 (omeprazole magnesium) for OTC Use

**Introduction**

Omeprazole is a proton-pump inhibitor (PPI) approved for prescription use in 1989. It is currently marketed for the following indications:

- For the treatment of duodenal and gastric ulcer;
- For the treatment of gastroesophageal reflux disease (GERD);
- For the maintenance of healing of erosive gastritis;
- For the long-term treatment of pathological hypersecretory conditions.

In this NDA submission, the sponsor has proposed the OTC marketing of Prilosec 1 for (1) the relief of heartburn (acutely); (2) the prevention of meal-induced heartburn; and (3) the prevention of symptomatic heartburn for 24 hours. In support of these indications, the sponsor presented 6 efficacy studies, 5 actual use studies, and 1 label comprehension study for review.

There are currently two classes of drug products available OTC for use in heartburn: antacids and acid reducers also known as histamine-2 receptor antagonists (H2AR). Both of these classes of drugs are indicated for the treatment of acute occasional heartburn symptoms. The acid reducers have the additional claim for the prevention of meal-induced heartburn at specified times depending upon the product. The 24-hour prevention claim is one not currently available in the OTC market.

**Background**

Astra Zeneca proposes to market Prilosec 1 as a 10 mg once a day OTC tablet to relieve acute symptoms or prevent heartburn related to a meal in addition to new OTC indication, 24-hour prevention of heartburn. In support of OTC use, the sponsor has submitted 6 new efficacy/safety trials, 5 actual use studies, and 1 label comprehension study. Of the efficacy trials, studies 092, 095, 017, 018 and 019 looked at the efficacy of 10 mg and 20 mg doses of Prilosec for acute heartburn relief. Studies 005 and 006 assessed the prevention of meal-induced heartburn, and studies 171 and 183 assessed the proposed 24-hour prevention claim. Safety was assessed from data presented in clinical trials and worldwide experience submitted for review by the sponsor. In addition, studies 003, 067, 014, 022 and 091 were performed to assess compliance to the recommended labeling. An additional label comprehension study (3358) was also performed to understand comprehension of the labeled directions.

## FDA Reviews

### *Efficacy*

#### Acute Relief

Studies 092 and 095 were submitted to the NDA to assess heartburn relief acutely. Both of these trials were placebo-controlled using Prilosec 10 mg and Prilosec 20mg to assess efficacy. The average heartburn severity on a scale of 0-3 (3=severe) was 1.8-1.9, with over 50% of those enrolled having a severity > 2. The primary efficacy endpoint sustained complete relief following first episode/first dose revealed no statistically significant differences between placebo and either dose assessed. The secondary endpoints were inconsistent. The "all episodes analysis" showed no benefit for current OTC occasional episodic usage. Of note, the results beyond the first episode were confounded by pharmacodynamic carry-over effect from prior doses. Further, almost 90% of enrollees took more than 3 doses.

Three additional heartburn relief studies (017, 018, and 019) were submitted to the IND. These studies assessed sustained complete relief, sustained adequate relief, overall assessment of study medications, and back-up medication. Again, no efficacy was obtained for any of these endpoints.

#### Prevention of Meal-Induced Heartburn

Studies 005 and 006 assessed doses of 10 mg and 20 mg of Prilosec for the prevention of meal-induced heartburn. The primary efficacy endpoint was the percent of subjects' heartburn-free 4 hours post-meal. In study 005, neither dose of omeprazole was significantly different from placebo, although the 20 mg dose trended towards significance with a p-value of 0.057. With regard to study 006, both 10 mg and 20 mg doses were significantly superior to placebo. Secondary endpoints of overall assessment of medication, maximum severity score, backup medication use, average symptom severity, and reduction of maximum severity score were supportive for the 20 mg dose. Only maximum severity score was supportive for the 10-mg dose.

#### 24-Hour Prevention

Studies 171 and 183 assessed 24-hour prevention of symptoms for up to 10 days at both 10 mg and 20 mg doses of Prilosec. Eligibility was heartburn greater than 1-month duration, heartburn at least 2 days per week, and OTC use of antacid or H2AR responsive heartburn in the past. The primary efficacy endpoint was heartburn-free on day 1. The results indicated statistically significant differences compared to placebo for both doses, with efficacy increases over time from day 1 to day 14. However, the benefit was lost within 3 days of discontinuation of therapy.

### *Biopharm Issues*

The pharmacokinetic/pharmacodynamic profile of Prilosec is useful in understanding the efficacy result above. The half-life of omeprazole is short, 0.5-1 hour. There is also a slow pharmacodynamic onset. A maximal inhibitory effect on pentagastrin stimulated acid secretion is 65% when measured 24 hours after administration of repeated once daily doses greater than 20 mg. There is, however, a long-acting pharmacodynamic effect of acid secretion reduction to baseline over 3-5 days. It is these effects that make Prilosec ineffective in acute relief and make it beneficial for 24-hour prevention.

With regard to drug-drug interactions, omeprazole interacts with drugs metabolized by the cytochrome P450 enzymes. Of these, CYP2C19 appears to have a more clinically relevant role, as this enzyme is lacking in "slow metabolizers" (15% Asian, 3% Caucasian). In these individuals, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, R-warfarin, resulting in increased AUCs for these drugs when administered concomitantly. A dose-dependent inhibition of diazepam metabolism by omeprazole has been suggested in some of the data reviewed by the Pharmacokinetic Reviewer. Thus, caution needs to be exercised when co-administering with these drugs and dosage adjustments may be indicated.

In patients with chronic hepatic disease, a decreased first-pass effect and increase in plasma half-life to 3 hours has been demonstrated at doses of 20 mg of omeprazole. In addition, a four-fold increase in AUC

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was noted in some Asians compared to Caucasians for the same dose of omeprazole, which has been attributed to "slow metabolizer" state. For these populations, the prescription labeling has recommended dosages adjustments.

Additional dosage adjustments have been suggested in the prescription labeling for Prilosec for those individuals taking drugs that depend on gastric pH for bioavailability. For drugs, such as ketoconazole, digoxin, and iron salts, omeprazole may interfere with absorption, increasing absorption of digoxin while decreasing the absorption of ketoconazole.

### *Safety*

The areas of major concern are hematologic effects, liver toxicity, anaphylaxis, and drug-drug interactions. To assess safety, data was evaluated from the clinical and actual use trials, post-marketing surveillance reported to the FDA and worldwide sources, and the medical literature.

The frequency of adverse events (AE) reported in the clinical trials were similar to those known for the prescription products, with regard to headaches (5%), infection (2%), and diarrhea (2%), without dose-related differences. More serious adverse events, consisting of hepatotoxicity, agranulocytosis/marrow suppression, angioedema/anaphylaxis, and drug interactions were also described. Most of these reactions were, again, not dose-dependent, and were transient in nature. There were reports, however, in the worldwide databases that indicated rare fatalities in each of these categories for the currently marketed products.

### GERD (Gastroesophageal Reflux Disease)

Because of the pharmacokinetic/pharmacodynamic nature of omeprazole and efficacy supporting the proposed indication of prevention of symptomatic heartburn for 24 hours, the implication of long-term exposure was also raised in terms of masking and/or delay in diagnosis of GERD complications and malignancy and effects of exaggerated rebound of gastric acid secretion. Known complications of GERD are Barrett's esophagitis (1-6%), erosive esophagitis (2.4-47%), Barrett's esophagus with dysplasia (<1%), and esophageal adenocarcinoma (<1%). The short-term use of omeprazole in an OTC heartburn population is unlikely to pose an increased health risk or mask serious diseases. The long-term or chronic use of omeprazole would pose the same risks to the consumer population as that seen in the prescription population with regard to masking of more serious conditions or with regard to rebound effects.

### Pregnancy Category

Pregnancy Category C is the recommended designation; based on the effects on the human fetus, especially developmental and behavioral, which have not been adequately defined. Based on the mechanism of action of the drug and the consistent results amongst several animal species, exposure to pregnant women should be limited. It is unclear how this would be accomplished in the OTC setting.

### *Actual Use Studies*

Five actual use studies were performed to assess usage patterns under OTC-like conditions. Three of these were self-selection and usage studies (Study 003, 067, and 022) and two were marketing and usage studies (Study 014 and 091). Studies 003 and 022 enrolled individuals over the age of 12; whereas studies 014 and 018 enrolled people over the age of 18. Study 067 assessed adolescent use and compliance in the 12-17 year old group. In all cases pregnant or lactating females, those with active peptic ulcer disease (PUD) on H2ARs or PPIs, phenytoin, warfarin, diazepam, clarithromycin, those having known hypersensitivity, continuous abdominal pain for >10 days, or dysphagia, were excluded from enrollment. The study label described the indicated uses for the product.

For the three self-selection trials (003, 067, and 022), usage pattern was assessed for the following parameters: prevention any time, prevention 1-hour before a meal, dual prevention, relief, and prevention and relief. In addition, assessments were made for correct use: taking 1 tablet per day, taking 1 dose per day, and taking for no more than 10 consecutive days. In all three studies, approximately 25-42% of participants did not use the product consistently with dosing directions. In the prevention only groups, 64% used for more than the 10-day limit. Approximately 19-28% in the prevention and relief group used the

product for more than 10 days. Overall, 58-75% of participants in the 3 studies dosed according to all 3 dosing directions. Relief Only users were more compliant than Prevention Only users, and the Prevention Only users were the most non-compliant in terms of exceeding the maximal 10-day sequential use limit. This is of concern, since efficacy was not demonstrated for this group of Relief Only users. It is worth emphasizing again, that the efficacy in the clinical trials discussed above was demonstrated only as prevention therapy.

#### **Labeling Comprehension**

The label comprehension study was performed as a mall intercept trial, to assess comprehension to the labeled directions in 4 cohorts of individuals: heartburn sufferers (N=197), heartburn non-sufferers (N=104), low literate (<8<sup>th</sup> grade reading, N=54), and must ask doctor before use (N=117). When asked the purpose of the product, 65% thought the product was for relief, 18% for prevention, and 16% for prevention and relief, clearly showing that the majority of people did not understand the intended use of the product. Comprehension was in the 80% range for the following items: understanding what to do after 14 days of use, understanding what to do if having difficulty swallowing, and understanding when to take omeprazole to prevent expected stress or meal induced problems. However, the low literacy group has a comprehension level of 75% with regard to the latter issue, of when to take omeprazole to prevent expected stress or meal induced problems. Additionally, the low literacy group has a level of comprehension of 75% for when to see a doctor prior to use. Even though the labeling comprehension trials suggested that at least 75% of people understood when to contact a doctor prior to use, the results indicated that these same people may not actually do so.

An additional study, referred to as the addendum study, was conducted, in 60 men and women, to determine whether the high proportion of people in the Special Population Cohort who incorrectly responded that they would use the product without seeing a doctor was due to a wording problem or a true reflection of how they believed they would use the product. The results of this study indicated that 81% of participants at risk correctly identified that a doctor should be seen prior to use. However, the response rate to scenario questions varied depending upon how the question was asked. This suggested that although the warnings on the label may be understood, it is not clear that people who need to see a doctor will actually do so.

Following the label comprehension trial, a new label was devised. However, this label and the one proposed in the NDA were never tested.

#### **Discussion**

As is clear from the data presented in the NDA submission, there are some very specific issues that need to be addressed prior to considering the safe and effective use of Prilosec 1 in the OTC setting. First, given the pharmacokinetics and pharmacodynamics of this product, Prilosec 1 is not indicated for acute symptomatic relief of heartburn. Despite a relatively short half-life of 2 hours, the pharmacodynamic effect is due to its persistent drug effect of 3-5 days after administration, which can be explained by its mechanism of action. This mechanism of action has been described as an irreversible inhibition of the proton pump, which has a half-life of 50 hours. It is this feature that makes this product not very successful for first dose affect in relieving acute heartburn pain. However, it is the prolonged pump inhibition that makes this a successful product for repeated (chronic) administration.

Despite the results from the clinical trials, indicating efficacy for prevention of symptoms for 24 hours at both the 10 mg and 20 mg omeprazole dose, and for prevention of consuming food and beverages for the 20 mg dose, the actual use and label comprehension trials indicate that consumers do not have a clear understanding of when this product should be used. This is clearly demonstrated by the results of the actual use trials showing that compliance was better for relief only users, which is the group in which efficacy was not demonstrated from the clinical trials. Further, the label comprehension trials failed to demonstrate that consumers understand the nature of prevention implied by labeling. Further, the actual

use and label comprehension trials failed to study how this product should be used OTC by consumers in contrast to those products currently available for relief and for prevention and relief.

In addition, the sponsor failed to provide adequate data to demonstrate that drug-drug interactions, which are delineated in the prescription labeling, are not relevant to the OTC consumer for safe use of this product. They further were unable to demonstrate that consumers understand which drugs should not be used concurrently.

The remainder of the safety profile is not dissimilar to that of the currently marketed prescription product. However, the sponsor again has failed to provide data to substantiate consumer understanding of when to seek professional intervention.

When looking at the application in toto, it is clear that this product may have merits in an OTC environment; however, the data as presented would not support OTC marketing at this time. Issues that remain to be addressed include: 1) duration and chronicity of use; 2) consumer's ability to follow directions and understanding of when to seek physician or health care input for assessments from both an efficacy and safety stand-point; 3) long-term implications of missed diagnosis, especially with regard to Barrett's esophagitis and carcinoma risk; 4) consumers' understanding of the specific treatment goal; 5) issues regarding possible dose titration; and 6) the specific population in which product can be used.

### **Conclusions**

The application for marketing of omeprazole for OTC use should not be approved at this time. The sponsor has not provided sufficient evidence to support the safe and effective use of this product in the OTC market and that consumers understand how this product should be used. With further studies, it is possible that the sponsor may be able to identify the appropriate OTC population who would likely receive benefit; however, as this product would necessitate chronic use, the safety of use with regard to drug interactions, serious adverse events, and long-term consequences of misdiagnoses must be carefully delineated.

### **Recommendations**

In order to consider this product for OTC use, the actual role for this product must be made clear by the Sponsor. As proposed, there is no place for this product for acute relief (first dose effect) OTC. However, as a product to be used for prevention there may be a place. The onus is upon the Sponsor to demonstrate that consumers would understand when and how to use this product, which is different from the currently available OTC heartburn products. This would necessitate performing additional label comprehension and actual use trials, to make certain that consumers understand the label, especially regarding when and why to seek professional assistance, drug-drug interactions and long-term consequences of use. Of note, the label comprehension trial(s) should provide the labeling that will assess consumers understanding and ability to achieve desired goals.

The specific nature of the clinical trials to be conducted would depend upon the dose of Prilosec desired in the OTC market place. Clinical trials of longer duration using an OTC population would also be indicated particularly since there is no data to support efficacy of 10 mg beyond 14 days for prevention claims. If 10 mg is the desired dose, clinical efficacy trials and/or literature to support efficacy for meal-induced heartburn prevention would be needed, as the data presented in the NDA submission are inconsistent for that indication at that dose. If 20 mg were the desired dose, clinical trials, designed as actual use trials, would be needed to demonstrate safety in an OTC population under OTC-conditions of use. Further, the 10-day limitation to use does not make sense, as this product to be used effectively needs to be administered chronically. Again, the onus is upon the sponsor to demonstrate that consumers understand the risks and benefits of chronic use and when they need to return to a health care provider for medical assessment.

Additional recommendations may be forthcoming.

[ 15/ ]  
(Linda M. Katz, M.D., M.P.H.)

cc: orig to NDA 21-229  
HFD-560/ganley/katz/keravich  
HFD-180/talarico/walsh  
HFD-005/delap/bull  
HFD-003/houn/raczkowski

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NDA 21-229

DISCIPLINE REVIEW LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

NOV 2 1999

Dear Dr. Kozarek:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

Our review of the chemistry section of your submission is complete, and we have identified the following deficiencies:

1. Please be advised that DMF \_\_\_\_\_ for the drug product has been found to be deficient and the holder has been notified.
2. Please provide a complete set of specifications for the drug substance and the drug product in the NDA.
3. Please provide a complete methods validation package (3 copies).
4. Please be advised that DMFs \_\_\_\_\_ and \_\_\_\_\_ have been found to be deficient and the holders have been notified.

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 Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

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Sincerely,

/s/

Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal and Coagulation Drug  
Products, (HFD-180)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

-----  
Liang Zhou

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MEMORANDUM

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

DATE: October 23, 2000

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

[ ISI ]  
October 31, 2000

SUBJECT: NDA 21-229, PRILOSEC 1™ (omeprazole magnesium) tablets for OTC use:  
Recommendations for Regulatory Action

TO: Director, ODEV, HFD-105  
Director, ODEIII, HFD-103  
Deputy Director, ODEIII, HFD-103

THROUGH: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 /S/ 11-3-0

**I. Background/Introduction**

Prilosec (omeprazole) Delayed-Release Capsules (OME) is a prescription drug product approved for several indications including the short-term treatment of symptomatic gastroesophageal reflux disease (GERD), the short-term treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The proposed over-the-counter (OTC) formulation, PRILOSEC 1 (omeprazole magnesium) tablets (OME-Mg), uses the alkaline magnesium salt of omeprazole in a tablet containing individually enteric coated pellets (i.e. multiple unit pellet system-MUPS).

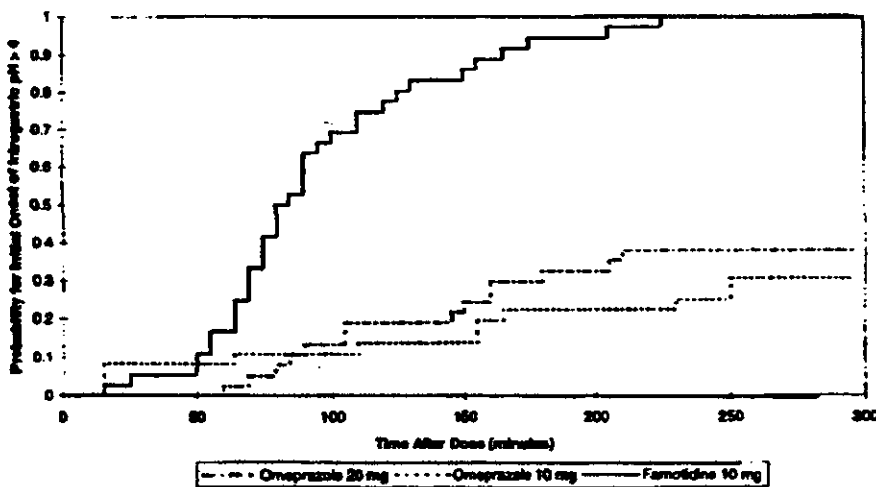
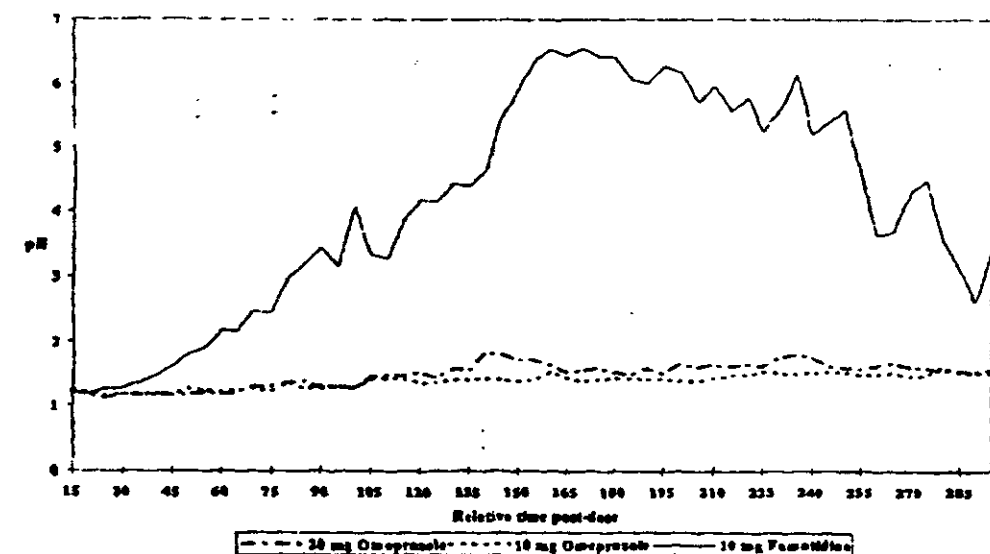
OME belongs to the proton pump inhibitor (PPI) class. PPIs are substituted benzimidazoles which irreversibly inhibit the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme system ("proton pump") located at the apical membrane of the parietal cell. OME is a pro-drug and a lipid-soluble weak base that, at neutral pH, is devoid of gastric acid inhibitory effect. Following its systemic absorption, the PPI reaches the parietal cell, becomes protonated (ionized) and rearranges to form a sulphenic acid and sulfenamide. The sulphenamide reacts covalently with the sulphhydryl group of the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme system to inhibit gastric acid secretion.<sup>1</sup>

- OME exhibits short PK half-life (0.5 to 1h), slow PD onset (acid inhibition of only 50% of maximum at 24h) and exhibits long-acting PD effect.
- OME's prolonged inhibition of gastric acid secretion (to any stimuli) is delayed for a few hours, stabilizes after 3 to 4 days and returns to baseline within 3 to 5 days.

<sup>1</sup> The reactions of the PPI with the enzyme is permanent and new H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme needs to be formed to allow the resumption of gastric acid secretion.

- Because of the above-summarized PD properties, OME is not considered suitable for the indications being sought by the sponsor: relief of heartburn, acid indigestion and sour stomach and prevention of these symptoms brought on by consuming certain food and beverages. These indications require **rapid onset of action**, which is provided by either acid neutralizers (antacids) or antisecretory drugs, the latter at a fraction of the approved daily prescription dose for non-prescription H<sub>2</sub>-receptor antagonists (H<sub>2</sub> RAs). This difference in onset of secretory action is clearly illustrated in Fig. 1 (Astra Merck Protocol 129).

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\* Graph presents (1 - Kaplan-Meier estimates).

Fig. 1 - Median 5 min intragastric pH values postdose by treatment (top graph)  
Kaplan-Meier estimates for the time to onset of intragastric pH > 4 by treatment (bottom graph)

Table 1 shows that the dose of H<sub>2</sub>RAs required to heal erosive esophagitis (EE) is usually higher than that required to relieve symptoms of symptomatic GERD (s-GERD).

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**TABLE 1**

**Doses/regimens of H<sub>2</sub>-RAs for Treatment of GERD vs EE in Comparison to OTC Doses**

|                                                                                                                                                                                                       | OTC Dose (mg) | Relief of Symptoms of s-GERD     | Healing of and Relief of Symptoms of EE                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|----------------------------------|------------------------------------------------------------------------------|
| Cimetidine (TAGAMET)                                                                                                                                                                                  | 100           |                                  | 1600 mg daily in divided doses (800 mg b.i.d. or 400 mg q.i.d. for 12 weeks) |
| Ranitidine (ZANTAC)                                                                                                                                                                                   | 75            | 150 mg b.i.d. <sup>a</sup>       | 150 mg q.i.d. <sup>b</sup>                                                   |
| Nizatidine (AXID)                                                                                                                                                                                     | 75            |                                  | 150 mg b.i.d. (up to 12 weeks)                                               |
| Famotidine (PEPCID)                                                                                                                                                                                   | 10            | 20 mg b.i.d. (for up to 6 weeks) | 20 or 40 mg b.i.d. (for up to 12 weeks)                                      |
| a) Symptomatic relief commonly occurs within 24h after starting therapy with ZANTAC 150 mg b.i.d.<br>b) Symptomatic relief commonly occurs within 24h of therapy initiation with ZANTAC 150 mg q.i.d. |               |                                  |                                                                              |

- The data on H<sub>2</sub> RAs in Table 1, are to be contrasted with that for PPIs, including OME, approved for the same indications (Table 2).

**TABLE 2**

**Doses of PPIs for Treatment of s-GERD vs EE in Comparison to Proposed OTC dose for OME**

|                                                                                                                                                                                                                                      | Proposed OTC Dose | Relief of Symptoms of GERD           | Healing of and Relief of Symptoms of EE           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------------|---------------------------------------------------|
| Omeprazole (Prilosec)                                                                                                                                                                                                                | 20 mg             | 20 mg (for up to 4 weeks)            | 20 mg (for 4 to 8 weeks)                          |
| Lansoprazole (Prevacid)                                                                                                                                                                                                              | N/A               | 15 mg once daily (for up to 8 weeks) | 30 mg once daily <sup>a</sup> (for up to 8 weeks) |
| a) For patients who do not heal with Prevacid for 8 weeks (5 to 10%), it may be helpful to give an additional 8 weeks of treatment.<br><br>If there is a recurrence of EE an additional 8-week course of Prevacid may be considered. |                   |                                      |                                                   |

**NOTE:** Whereas the daily doses of drug needed to heal EE with either H<sub>2</sub> RAs or PPIs are higher than those needed to relieve symptoms of s-GERD, the recommended dose of OME for the two prescription indications, as well as the proposed OTC dose, is the same (20 mg per day).

## II. Brief Regulatory History

**NOTE:** Only key events are listed.

### IND

- Submitted 12/21/83                      • Indication: Treatment of Duodenal Ulcer
- Clinical Hold 7/18/84  
7/18/84 letter to sponsor states they had reported preliminary histopathological data from a 2-year carcinogenicity study of omeprazole in rats. These preliminary results indicated an increased number of tumors in rats.

FDA concurred with the sponsor's decision not to initiate planned clinical investigations until these findings were clarified.

- Remove clinical hold 9/23/85  
[pharm/tox review of 7/12/85; minutes of 8/6/85 meeting and letter to sponsor, 9/23/85]. It was agreed that the carcinoid issue seemed related to acid inhibition and its duration. Nonetheless, the safest dose to be chosen was the smallest dose. It was clear that gastrin plays a role in hyperplasia of the EC-L cell. Short-term studies were allowed. Animal findings were to be disclosed in the consent form.
- Pre-NDA meeting (minutes 12/17/87)

### NDA 19-810

- Submitted 12/23/87 for marketing of omeprazole for the following indications: treatment of duodenal ulcer, treatment of gastroesophageal reflux disease, hypersecretory conditions.
- Refusal to file 2/10/88. Requested was more information on EC-L cell hyperplasia
- NDA resubmitted on 6/30/88
- Approval for the indication treatment of GERD is recommended
- Not approvable 11/2/88  
(Chemistry deficiencies)

Approvable: 7/27/89

Approval: 9/14/87

Indications for which omeprazole has been approved include treatment of symptomatic GERD (20 mg once-a-day) and treatment of erosive esophagitis (20 mg once-a-day).

- There have been 2 GI Advisory Committee meetings to discuss long-term safety.
- Black box including pre-clinical data related to carcinoids has been removed.

### III. Proposed Prilosec 1 OTC Indications

1. Treatment of acute occasional heartburn, acid indigestion and sour stomach.
2. Prevention of meal-induced heartburn, acid indigestion and sour stomach.
3. \_\_\_\_\_

- **To prevent symptoms:** swallow one tablet with a glass of water any time during the day, or if you prefer, one hour before those events associated with occasional heartburn, such as consuming food or beverages, stress, hectic life style, lying down, or exercise.

It must be noted that 24h prevention is a new indication for OTC heartburn treatment and is not episodic. Similarly, non-meal related symptom prevention is a new indication. In addition, the proposed dose (20 mg) is the same as the prescription dose for GERD (20 mg for s-GERD and 20 mg for EE).

**NOTE:** The need to differentiate **episodic HB** (the symptom) from \_\_\_\_\_ was already brought to the sponsor's attention at an April 29, 1998 meeting held for the purpose of discussing the design of an Actual Use Study and the proposed labeling for the trial.

\_\_\_\_\_

\_\_\_\_\_

### IV. Reviewers

Owing to the magnitude of NDA 21-229 and the numerous issues that needed to be addressed regarding the switch from prescription to OTC omeprazole, reviewers from many disciplines were involved<sup>2</sup> primarily the GI and the Division of Over-The-Counter Drugs.

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<sup>2</sup> These included L. Goldkind (Efficacy), M. Avigan (General and Special Topics of Safety), S. Kress (Visual Disturbances, Hearing and Vestibular disorders, skin and appendices), S. Al-Fayoumi (Biopharm), T. Robison (Pharmacology/Toxicology), W. Chen (Biostatistics), A. Shaw (Chemistry), L. Chin and D. Shetty (Actual Use Studies), K. Lechter (Label Comprehension Study), A. Corken (Spontaneous Reporting System data) and Hugo E. Gallo-Torres (Multidisciplinary; this review).

## V. Summary Review of the Evidence

### A. Efficacy/Statistics

The sponsor presented results of six (6) well-designed and well-controlled studies, two for each of the three indications being sought (Tables 3, 4 and 5).

#### 1. Indication1: Episodic HB Relief (Treatment of HB):

The efficacy results of studies 092 and 095 are summarized in Table 3.

**TABLE 3**

#### Episodic HB Relief (Treatment of HB)

|                                                                                                                                      | OME (mg/d)     |                |                | Therapeutic gain/[p-value] |                |                |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|----------------|----------------------------|----------------|----------------|
| Study 092                                                                                                                            |                |                |                |                            |                |                |
|                                                                                                                                      | PL<br>{n=627}  | 10<br>{n=620}  | 20<br>{n=620}  | 10<br>vs<br>PL             | 20<br>vs<br>PL | 20<br>vs<br>10 |
| Responders <sup>a</sup>                                                                                                              | 185<br>(29.5%) | 195<br>(31.5%) | 187<br>(30.2%) | 2%<br>[N.S.]               | 0.7%<br>[N.S.] | NONE           |
| Study 095                                                                                                                            |                |                |                |                            |                |                |
|                                                                                                                                      | {n=602}        | {n=623}        | {n=627}        |                            |                |                |
| Responders <sup>b</sup>                                                                                                              | 177<br>(29.4%) | 186<br>(29.9%) | 183<br>(29.2%) | 0.5%<br>[N.S.]             | NONE           | NONE           |
| a,b) The primary efficacy endpoint was the sustained complete relief for the first treated episode of HB (first dose) (ITT analysis) |                |                |                |                            |                |                |

### Summary of Findings

#### (Primary Efficacy Analysis)

- Mean frequency of HB: 60% of days
- Average HB severity: 1.8 to 1.9 (Scale 0 to 3: moderate=2)
- Over 50% of subjects had HB severity  $\geq 2$
- 3 Additional HB Relief Studies (017, 018 and 019):
  - 11,700 subjects enrolled

- No efficacy at study endpoints:

Sustained complete relief  
 Sustained adequate relief  
 Overall assessment of study medication  
 Backup medication

**Conclusions**

- 1) 5 studies of episodic HB relief: Primary analyses all failed
- 2) "All episodes analysis" failed to demonstrate efficacy for occasional episodic usage

**2. Indication 2: Prevention of Meal-Induced HB (4-h prevention of HB)**

The efficacy results of Studies 005 and 006 are summarized in Table 4.

**TABLE 4**

**Prevention of Meal-Induced HB**

|                                                      | OME (mg/d)    |                |                | Therapeutic gain/[p-value] |                 |                |
|------------------------------------------------------|---------------|----------------|----------------|----------------------------|-----------------|----------------|
| <b>Study 005</b>                                     |               |                |                |                            |                 |                |
|                                                      | PL<br>[n=423] | 10<br>[n=428]  | 20<br>[n=433]  | 10<br>vs<br>PL             | 20<br>vs<br>PL  | 20<br>vs<br>10 |
| Responders <sup>a</sup>                              | 85<br>(20.1%) | 104<br>(24.3%) | 110<br>(25.4%) | 4.2%<br>[N.S.]             | 5.3%<br>[N.S.]  | 1.1%<br>[N.S.] |
| <b>Study 006</b>                                     |               |                |                |                            |                 |                |
|                                                      | [n=390]       | [n=387]        | [n=393]        |                            |                 |                |
| Responders <sup>b</sup>                              | 67<br>(17.2%) | 98<br>(25.3%)  | 101<br>(25.7%) | 8.1%<br>[0.005]            | 8.5%<br>[0.004] | 0.4%<br>[N.S.] |
| a,b) Primary Efficacy Endpoint: HB-free 4h post-meal |               |                |                |                            |                 |                |

**Conclusions**

- 1) Prilosec 1 at 20 mg dose *may have marginal efficacy* for the prevention of HB when taken 1 hour before HB-inducing meal
- 2) Prilosec 1 at 10 mg dose *lacks replicated efficacy* for primary and most meaningful secondary endpoints

**Outstanding issues**

- 1) Unreplicated results
- 2) Small therapeutic gains compared to placebo
- 3) Consumer confusion due to lack of benefit HB relief
- 4) Pharmacodynamics favor chronic use

**3. Indication 3: 24-h Prevention: Studies 171 and 183 (Table 5)**

**Initial Comments**

- **New indication: 24-hour prevention of symptoms for up to 10 days (Prevention of further HB episodes).**
- **The MO (Dr. Goldkind) believes and this reviewer agrees that this new indication represents management of GERD.**

**Entry Criteria**

- **HB of greater than 1 month duration; frequency: at least 2 days per week**
- **Antacid or OTC H<sub>2</sub>RA responsive HB in the past (enriched population)**

**Demographics**

- **80% of subjects: baseline frequency  $\geq$ 50% of days**
- **Mean severity 1.5 (2=moderate severity)**

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countries, with 90 million courses in the U.S. The indications for use have included the various labeled acid-related GI disorders and other off-labeled conditions. Although the safety experience with prescription omeprazole is generally reassuring, an important question is whether the safety profile of the drug is suitable for OTC use (see below). OME-Mg is approved for prescription use in 26 countries<sup>3</sup>; it is available under the trade names of LOSEC, LOSEC tablets, and LOSEC MUPS, since February of 1998. The present review is based, primarily, on Dr. Avigan's Safety review of NDA 21-229; his and the sponsor's presentations at the October 20, 2000 Joint Advisory Committee meeting; and discussions of safety at the same meeting.

The safety information for the proposed OTC indications is derived from three sources: a) OTC clinical trials (n=8,179) where subjects were administered 10 or 20 mg daily doses of the drug for 1 to 14 days; b) information from prescription clinical trials (n=5,757) where patients were administered 10 to 40 mg daily doses of the drug for 1 day to 12 weeks; and c) two Post-Marketing Surveillance Databases: SafeTNet (n=15,385) until 6/30/98 and OME-Mg (2/98 to 12/99). The main safety findings from each of these sources are briefly discussed below. In addition to general safety issues, the following special areas will be considered: drug-drug interactions, special populations (adolescents, pregnant women), safety profile under long-term (>12 weeks) conditions of use which includes masking of disease, tumorigenicity and gastric acid rebound. At the end of this section, a succinct discussion and the actual voting on safety issues at the October 20, 2000 AC meeting, is included.

- The safety experience from OTC trials is characterized by brief exposure (up to 14 days) to the drug and short-term monitoring of AEs. These are conditions where rare AEs may not be detectable. In addition, adolescents (aged 12 to 17y) and Asian Americans (n=105 and 48, respectively) are under represented in this database. The following incidences were noted:

|                   |         |
|-------------------|---------|
| Headache          | 5%      |
| Infection         | 2%      |
| Diarrhea          | 2%      |
| Serum Sickness    | 1 case  |
| Urticaria         | 4 cases |
| Elevations of AST | 7 cases |

In the OTC trials there were no dose-related differences. The drug was withdrawn in 13 patients [headache, n=10; rash, n=3]. Two deaths were reported, neither related to the drug.

The conclusion is reached that the AE profile of the drug, under these OTC conditions, is similar to the (mostly short-term) prescription experience.

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<sup>3</sup> OME-Mg is available in Canada as a prescription delayed-release (enteric-coated) tablet, which is a different formulation than the MUPS formulation. OME-Mg is approved for OTC use only in Sweden, available as LOSEC MUPS since early 2000. OME-Mg MUPS has never been marketed in the U.S. and is the proposed formulation for OTC marketing.

- As requested by the Division, the sponsor addressed many areas of safety in NDA 21-229. These are addressed in detail in Dr. Avigan's safety review of this NDA. Only salient points, addressed during Dr. Avigan's presentation at the October 20, 2000 AC meeting are highlighted here.

The four main areas of short-term toxicity relate to 1) liver injury; 2) agranulocytosis/bone marrow suppression; 3) angioedema/anaphylaxis; and 4) drug-drug interactions.

- With regard to liver injury, no dose-dependent toxicity was reported in a total of 9 trials (n=1,409), where patients (primarily GERD-related indications) were administered omeprazole for between 1 to 60 weeks. Between 2/1000 and 5/1000 treated patients developed LFT abnormalities (elevation of transaminases  $\geq 3$  x normal). Most abnormalities were mild and transient.

The post-marketing liver toxicity data from SafeTNet include: a) 33 fatal cases, two in which there was no other explanation of causality ("A" rating) and b) 227 non-fatal serious cases, 4 of which were assigned "A" rating (2 positive rechallenges). The FDA Adverse Event Reporting System (AERS) includes 2 liver transplants.

It is important to note that the currently approved labeling for PRILOSEC includes the following pertinent information in the ADVERSE REACTIONS section:

*Hepatic: Mild and, rarely, marked elevations of liver function tests ALT (SGPT), AST (SGOT),  $\gamma$ -glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice). In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal) and hepatic encephalopathy.*

In summary, omeprazole is a **hepatotoxin**. But the number of very serious AEs is rather small in the prescription arena. The switch from prescription to OTC should consider the possibility of drug-drug interactions with other OTC available hepatotoxins (i.e. acetaminophen), in an uncontrolled environment.

- The SafeTNet database includes 49 cases of toxic epidermal necrolysis and Stevens-Johnson syndrome, 2 assigned an "A" rating (1 fatal, 1 non-fatal). These cases are characterized by a variable time between exposure and onset of symptoms.
- In U.S. trials, the incidence of white blood cell suppression has been:
  - granulocytopenia           0.2% to 0.7%
  - leukopenia                 0.9% to 1.5%

Incidences from the Intensive Medical Monitoring Program (New Zealand) are:

- granulocytopenia       0.03%
- aplastic anemia         0.01%

White blood cell suppression SafeTNet experience includes: a) 26 fatalities, 5 of which were assigned an "A" rating; and b) 96 serious non-fatal cases, 35 of which were assigned an "A" rating.

Again, it is of interest to note that the currently approved labeling for PRILOSEC includes the following pertinent information in the ADVERSE REACTION section:

*Hematologic: Rare instances of pancytopenia agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.*

- Immediate hypersensitivity reactions have included angioedema/anaphylaxis, urticaria (1 to 2/1000), and wheezing. The incidence of angioedema/urticaria in the New Zealand Monitoring database is 0.46/1000. Serious hypersensitivity AES from the SafeTNet have included 134 cases of angioedema/anaphylaxis. Of these, 7 were fatal and 9 were assigned an "A" rating.

From the above, there is some concern about the occurrence of hypersensitivity reactions with prescription omeprazole (1/2000). This may contribute to the reluctance to switching from the prescription to the OTC arena.

- The Swedish Post-Marketing 1988-1999 voluntary reporting has included 219 AEs among prescriptions. Of these, 25 have been serious, non-fatal and 2 resulted in death. The serious non-fatal AEs included reports of reactions that were qualitatively similar to the U.S. experience: hypersensitivity reactions, liver toxicity, toxic epidermal necrolysis, interstitial nephritis and bone marrow suppression. The conclusion reached by Dr. Avigan, after appraising this information, is that there were no apparent differences between safety profiles of enteric-coated prescription formulation and magnesium formulation.
- With regard to drug-drug interactions, omeprazole interacts with the following cytochrome P<sub>450</sub> enzymes: CYP2C19 (lack of which in "slow metabolizers" is an important consideration), CYP3A4 (a minor pathway for omeprazole), CYP1A2, CYP2CP, CYP2D6 and CYP2E1. The general consensus is that although many interactions can be demonstrated, only a few are of clinical relevance. Included are those that may involve CYP2C19 "slow metabolizers" (3% Caucasians, 15% Asians), and where aging and liver disease may play an important role.
  - Omeprazole a) increases the absorption of digoxin and nifedipine by 10% to 26%, and b) decreases the absorption of drugs for which gastric pH is an important determinate of bioavailability. These include ketoconazole, itraconazole (80% decrease).
  - The information on "slow metabolizers" ("SM") can be briefly summarized as follows:

- 15 to 20% of Asians lack CYP2C19
  - $t_{1/2}$  longer than in "rapid metabolizers" ("RM") (2.1 vs 0.7h)
  - Area under the plasma concentration-time curve ca. 5-fold higher than "RM"
  - No drug accumulation because elimination  $t_{1/2}$  is short, relative to dosing interval
  - Labeled-prescription dose in Japan is same as in U.S.
  - In "SM" with hepatic impairment: a)  $t_{1/2}$  is longer than in "RM" (2.8 vs 0.7h); b) area under the plasma concentration-time curve is ca. 7-fold than "RM"; and c) there is no drug accumulation.
- Through CYP2C19 inhibition and reduced clearance, omeprazole induces 10% to 55% decrease in diazepam, phenytoin, R-warfarin

Again, it is important to keep in mind the above-summarized information when considering switching from prescription to OTC since "SM" or people with underlying medical conditions may have pronounced changes of CYP2C19 drugs.

- There are 2% of total prescriptions in the 11 to 20y old age group and children have - in general - not been included in clinical trials; omeprazole is not approved for prescription use in adolescents (patients under 18y of age). There were only 100 OTC study subjects under age 18 (17% of whom exceeded the 10-day limit) and a total of 39 cases in SafeTNet. From this information, the Medical Officer concluded that safety in adolescents has not been established because: a) age-related responses have not been studied; and b) age-related toxicities cannot be ruled out.
- There is some controversy with regard to omeprazole and genotoxicity, a subject matter that was amply discussed at the October 20, 2000 AC meeting.
  - *In vivo* and *in vitro* clastogenic effects in mouse and human bone marrow cells have been shown.
  - Chromosomal aberrations in human lymphocytes have been demonstrated.
  - Increased sister chromatid exchanges in peripheral lymphocytes of treated subjects was shown but this finding is yet to be confirmed (C. Thompson et al, 1991).
  - However, DNA mutagenicity as tested by the Ames Salmonella typhimurium test has been consistently negative. In addition, in certain animal models of cancer induction, omeprazole has been shown to prevent colon cancer induced by azoxymethane.
  - Omeprazole protects against colorectal carcinogenesis in the azoxymethane rat model, despite causing appreciable hypergastrinemia. This occurs by an unclear mechanism that merits further investigation.<sup>4</sup>

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<sup>4</sup> [I.D. Penman et al. Omeprazole inhibits colorectal carcinogenesis induced by azoxymethane in rats. Gut, 34:1559-1565 (1993)].

"Because of the compounding protective effects of omeprazole, this model is not a suitable one for studying the long-term trophic effects of gastrin on the colon".

A valid conclusion from the above information is that, due to possible genotoxicity, long-term exposure may be linked to increased risk of malignancy. Thus, additional (10 to 15 more years) experience is needed with the prescription formulation before it can be comfortably switched to OTC.

- Regarding use in **Pregnancy**, omeprazole is categorized as a "Class C" drug because of embryo-fetal and postnatal toxicity in animal models.<sup>5</sup> The drug has clastogenic properties.

- Although substantial human use has not revealed "signal", there is need for prospective or nested case control studies to properly characterize potential embryo-fetal damage in humans.

- Safety issues related to long-term use include: a) masking and/or delaying in the diagnosis of complications of GERD and malignancy; b) tumorigenic potential of drug-induced **hypergastrinemia** and the above-mentioned drug-related genotoxicity; c) exaggerated rebound of gastric acid secretion/recurrence of esophageal lesions upon drug discontinuation; and d) issues specifically related to long-term OTC use of omeprazole in GERD.

- a) There have been 49 gastric malignancy cases in SafeTNet (4/49 delay in diagnosis). The delay in diagnosis may be caused by temporary alleviation of symptoms and improvement in the appearance of endoscopically evaluated lesions.

GERD complications of important public health consideration include:

1. Barrett's esophagus<sup>6</sup> (up to 10% of GERD patients, according to Dr. Donald Castell's presentation to the October 20, 2000 AC), in which the symptoms are not distinguishable from GERD, and
2. Advanced stages of erosive esophagitis (2.4 to 47%), in which the medical management is aggressive suppression of gastric acid secretion.

- b) Another unsettled subject is that of PPI-induced **hypergastrinemia**. The facts, as listed by the Medical Officer, can be summarized as follows:

- 2-4 fold increases in serum gastrin concentrations are common
  - Elevated levels reverse upon stopping
  - Increases not observed with "low dose" H<sub>2</sub> receptor antagonists

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<sup>5</sup> These include rabbit embryo-fetal lethality, reduced rat fetal weights, reduced survival/growth and slowed behavioral development in rat offspring.

<sup>6</sup> Barrett's esophagus with dysplasia occurs in <1% of patients. Delay in diagnosis would prevent surveillance. Esophageal adenocarcinoma occurs in <1% of patients. Delay in diagnosis would reduce the chances of survival.

- Pronounced hypergastrinemia occurs in "outliers".
  
- Serum gastrin increase may be pronounced when the following conditions are present:
  - H. pylori infection
  - CYP2C19 polymorphism (SM/EM or SM/SM)
  - High dose and increased frequency of treatment
  - Low pretreatment gastric acid secretion state.

Numerous authors<sup>7</sup> have called attention to the trophic effect of gastrin on the gastrointestinal mucosa. The subject of whether hypergastrinemia is dangerous to man was amply discussed in Dr. Gallo-Torres' review of NDA 20-918 for omeprazole.

The trophic effect of gastrin was previously regarded primarily as a property unique to gastric enterochromaffinlike (ECL) cells. But other studies have demonstrated that gastrin stimulates not only the growth of normal gastrointestinal epithelial cells, but also *malignant* adenocarcinoma cell lines of colorectal, gastric, and pancreatic etiology<sup>8</sup>. Moreover, a recent large epidemiologic study by Thorburn et al. [*Gastroenterology* 115:275-280 (1998)] found that *prolonged hypergastrinemia comprises a risk factor for the development of certain GI malignancies, including colorectal cancer*. These studies all suggest (but do not prove) a potential role for gastrin in the pathophysiology of these malignancies of the gastrointestinal tract, whereby not only elevated levels of circulating gastrin, but also tumor-derived gastrin could provide a stimulus for the growth of such tumors. Several studies have demonstrated the presence of both  $\alpha$ -amidated gastrin and nonamidated gastrin precursors in colorectal neoplasma. Furthermore, both forms are potent mitogens and may exert their effects by binding to separate distinct receptors [C. Sova, *Science* 265:410-412 (1994)].

Despite the above-mentioned evidence that gastrin may play an integral role in promoting colorectal tumor growth, as well as malignancies throughout the GI tract, the precise mechanisms by which gastrin mediates its trophic properties have not been elucidated. In

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<sup>7</sup> L.R. Johnson et al. Mucosal DNA Synthesis: a short-term index of the trophic action of gastrin. *Gastroenterology* 67:453-459 (1974).

T.E. Solomon et al. Trophic effects of pentagastrin on gastrointestinal tract in fed and fasted rats. *Gastroenterology* 91:108-116 (1986)

T.C. Wang et al. Processing and proliferative effects of human progastrin in transgenic mice. *J. Clin Invest.* 98:1918-1929 (1996)

E. Malecka-Panas et al. Differential responsiveness of proximal and distal colonic mucosa to gastrin. *Peptides* 18:559-565 (1997).

G.S. Baldwin, A. Shulkes. Gastrin, gastrin receptors and colorectal carcinoma. *Gut* 42:581-584 (1998)

H. Nakata et al. Oncogenic Ras induces gastrin gene expression in colon cancer. *Gastroenterology* 115:1144-1153 (1998)

T.J. Koh et al. Overexpression of glycine-extended gastrin in transgenic mice results in increased colonic proliferation. *J Clin Invest* 1119-1126 (1999).

V.M. Stepan et al. Glycine-extended gastrin exerts growth-promoting effects on human colon cancer cells. *Mol Med* 5:147-159 (1999)

L.A. Dethloff et al. Inhibition of gastrin-stimulated cell proliferation by the CCK-B/gastrin receptor ligand CI-988. *Food Chem Toxicol* 37:105-110 (1999)

addition, previous studies aimed at determining a potential role for gastrin in carcinogenesis in the GI tract have yielded conflicting results. These studies involved either the measurement of serum gastrin concentrations in patients with colorectal cancer or conversely a determination of the number of individuals with hypergastrinemia who have colorectal cancer. Unfortunately, these studies have ignored the fact that gastrin is not *mutagenic*, but rather is *mitogenic*. This important hormone does not cause malignancies to arise, but it may stimulate the growth of pre-existing polyps and other GI tumors. Size comprises one of the most important factors in determining the biological behavior of colorectal polyps, and any factor that enhances polyp growth could thereby incite its malignant degeneration. In summary, there seem to be important unanswered questions regarding the potentially untoward effect of increased serum gastrin concentrations as a consequence of PPI (not just omeprazole) administration.

- There is no definite answer to the question of whether omeprazole is tumorigenic in humans. In addition to the two issues of concern already mentioned, genotoxicity and trophic effects of hypergastrinemia, there is potential for exaggerated growth promoting effects in *H. Pylori* infected individuals. This subject has been discussed at two GI Advisory Committee meetings.
  - The evidence to date of carcinogenicity (as summarized by Dr. Avigan) from clinical trials, SafeTNet and literature sources shows that: 1) ECL cell hyperplasia in humans, unlike rats, is not linked to carcinoid tumors; 2) there is no apparent causal relationship with carcinoid tumors and other GI malignancies; and 3) contribution in *H. Pylori* infected subjects to the development of gastric mucosal atrophy, intestinal metaplasia and dysplasia is not apparent.
  - There are, however, difficulties in determining the carcinogenicity of this PPI, including:
    - Limited number of subjects followed for longer than 1 year.
    - Lack of long-term prospective or nested cohort studies to track patients
    - Detection of malignancy - long lag phase
    - High background rates of malignancies - drown out weak 'signals'
    - SafeTNet - voluntary reporting
    - Lack of definition of high risk groups. As presented by Dr. Avigan, such subsets may be diluted by groups not at increased risk
- c) There is no question that rebound of gastric acid secretion occurs upon discontinuation of PPI and that this "biological response" is related to the administered dose. The following has been demonstrated with omeprazole:
  - Cessation of treatment is associated with rapid reappearance of erosive esophagitis
  - Acid rebound is reflected by increases in both basal - and pentagastrin - stimulated acid secretion
  - Acid rebound is self-limited

However, as noted by Dr. Avigan, whether acid rebound plays a role to extend usage has not been studied (but this is plausible); H. Pylori may influence the development of acid rebound. It is worth noting that pronounced acid rebound may not be detected in small studies.

One of the most convincing demonstrations of lesion/symptom recurrence upon discontinuation of omeprazole in GERD patients being treated with omeprazole long-term was reported by E.C. Klinkenberg-Knol et al. [Scand. J. Gastroent. 25:1144-1150 (1990)]. These authors studied the effects of sudden withdrawal of long-term maintenance therapy with omeprazole for up to 4 years. These patients showed prompt normalization of serum gastrin concentrations, and increased basal acid output. As a consequence, there was a fast recurrence of aggravation of GERD symptoms and endoscopically-proven signs of mucosal inflammation (erosive esophagitis).

#### **d) Issues related to long-term use of omeprazole in GERD.**

As mentioned above, the PD effects of omeprazole are long-lasting. With this PPI, maximal acid suppression occurs after 2 to 3 days of daily 20 mg doses. Based on several publications and due to the rebound of acid secretion, relapse of HB symptoms and/or esophageal inflammatory changes is predicted in some patients with GERD who discontinue treatment. Indeed, based on the frequency of HB, many subjects had GERD. In addition, in the actual use studies (see below) most subjects exceeded 10 days of use. Because of all of these considerations the possibility of treating GERD OTC was considered. To this end, input from outside consultants at the October 20, 2000 AC meeting was sought and obtained.<sup>9</sup>

#### **VI. Actual Use Studies**

These studies were reviewed by Ling Chin, M.D., M.P.H. and Daiva Shetty, M.D. A summary of their review, dated October 18, 2000 is included here.

- The clinical program conducted to support the labeling of OME-Mg for OTC use included data generated from 6 well-controlled clinical trials, 5 actual use studies, 1 label comprehension study, plus four additional at-home studies and global post-marketing information. The following studies were reviewed: 003, 067, 014, 022, and 091. Ca. 3500 subjects were enrolled into the 5 trials. Also reviewed was Global Post-marketing information for: (1) omeprazole magnesium MUPS tablet (European Rx experience, Swedish OTC experience) and (2) omeprazole magnesium Delayed Release Tablets (Canadian RX experience). It was noted that the sponsor has expanded the current HB indication for the OTC H<sub>2</sub>RAs from meal-induced HB to HB. They have also expanded the acute treatment of HB and the immediate prevention of a meal-induced HB episode to prevention of HB anytime within a 24-h time period.

<sup>9</sup> The following gastroenterologists participated in GERD discussion at the AC meeting of October 20, 2000: Drs. S. Cohen, M. Schuster, H. Waldum, M. Robinson and G. Sachs.

The reviewers noted that concerns about serious consequences arising from longstanding HB symptoms (e.g. esophageal strictures, Barrett's esophagus), have been discussed in recent literature. While no definitive line has been drawn to separate **episodic heartburn** from the disease entity, gastroesophageal reflux disease (GERD), the latter has been defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.<sup>10</sup>

The reviewers called attention to the fact that patient information provided by the American College of Gastroenterology advised that a doctor should be seen if symptoms of HB are not controlled with lifestyle modifications, OTC medicines are needed more than 2 times a week, or symptoms remain unresolved. The Updated Guidelines for the Diagnosis and Treatment of GERD, published in 1999, also called for further diagnostic testing if warning symptoms are present. The sponsor has stated that **episodic treatment of heartburn** is different from the treatment of gastroesophageal reflux disease (GERD). In this application, however, the proposed indication is for **prevention anytime within a 24-h period**. This, in essence, has changed the nature of the application from using a drug product for episode-linked prevention to prevention of any number of episodes of HB within a set time period.

The reviewers' conclusions are reproduced below:

1. Overall consistency of subjects with dosing directions was <80% (except Study #014, which had fewer tablets dispensed).
2. Relief-only users were more compliant with the dosing directions than the prevention only users.
3. Overall consistency by dosing occasions were much higher, i.e. each non-compliant subject is not non-compliant all of the time.
4. The majority of subjects took 1 tablet per dosing occasion and per dosing day.
5. Relief-only users were more compliant with the dosing day restriction.
6. The majority (65%) of prevention-only users exceeded the 10-day use limit.
7. Correctness of subjects' self-selection decision was not assessed.
8. Performance of subjects with respect to certain risk conditions cannot be assessed:
  - pregnancy
  - difficulty swallowing
  - persistent stomach pains (>10 days)
  - use of concomitant drugs

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<sup>10</sup> DeVault et al. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. Amer. J. Gastroenterol. 94:1434-1442 (1999)

9. Performance of subjects with respect to contacting a doctor or health care professional cannot be assessed.
10. Safety profile was unremarkable.

Actual Use Study 1998003,<sup>11</sup> (reviewed by Drs. Chin and Katz; October 17, 2000) led to similar conclusions.

## VII. Label Comprehension Study

Results from this trial and addendum study were reviewed by Karen Lechter, J.D., Ph.D. Dr. Lechter concluded that the data suggested potential for substantial use by persons who **should consult a physician first**. She commented that some information could benefit from strengthening, and noted that the sponsor **had not tested** the most recent label, which differed considerably from the tested label.

## VIII. Key Presentations the Non-Prescription Drug/Gastrointestinal Drugs (NPDGIAC) Joint Advisory Committee (October 20, 2000)

- The sponsor (Astra Zeneca/Proctor & Gamble) presentations included an overview by Dr. Donald O. Castell<sup>12</sup>, an expert in the field of PPI and GERD. Dr. Castell summarized the "iceberg concept" that pertains to all clinical disease and encompasses the spectrum of gastroesophageal reflux. The largest group consists of those who experience episodic, mild heartburn and treat it effectively with life-style changes, antacids or OTC H<sub>2</sub>RAs, but do not bother to visit a doctor with their complaints. The next largest group is those with symptoms for which treatment with PPIs or H<sub>2</sub>RAs is needed. The smallest group, at the tip of the iceberg, is those with symptoms, complaints and complications who must be treated with PPI long-term or surgery. These latter two groups are the ones visiting doctors. Those with the most severe esophagitis, endoscopically and histologically, have frequent episodes of reflux, longer intervals during which the esophageal pH remains below 4, and tend to have decreased lower esophageal sphincter pressures. This group of patients can be considered as having a mechanical disorder or may require surgical correction for restoration of sphincter competence. Symptoms may not be a good measure of disease severity, since progression of disease is seen in asymptomatic patients. Moreover, esophagitis may progress even with intensive therapy. In addition, the greater the severity of esophagitis, the lower the healing rate, and larger doses are often required for higher grades of esophagitis.

Dr. Castell mentioned a survey of 1004 individuals which demonstrated that the frequency of HB in these U.S. adults was 11% daily, 13% weekly, 18% monthly and 58% none. HB is the

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<sup>11</sup> "A multicenter, open-label, actual use study to investigate the consumer usage patterns/dosing compliance of omeprazole magnesium, 20.6 mg, when used by OTC consumers".

<sup>12</sup> The presentation by this esophagologist was entitled "Proton Pump Inhibition in the Self-Management of Heartburn".

common symptom and 50% of the individuals did not have esophagitis (they had s-GERD), 40% had EE, 10% had epithelial metaplasia and 0.5% patient-year had epithelial dysplasia or cancer. HB is the typical symptom of GERD. Although the severity of esophageal injury correlates with the degree and duration of acid exposure, the symptoms are poorly correlated with tissue damage. **He stressed that GERD usually recurs after effective treatment.** Dr. Castell concluded that: 1) candidate indications for OTC omeprazole were prevention of predictable occasional heartburn and management of occasional heartburn (2 of the 3 indications being sought by the sponsor); 2) the safety of long-term omeprazole has been established; and 3) masking of important disease is unlikely if properly labeled. Dr. Castell concluded his presentation by noting that this approach may bring more HB patients to physicians.

- The FDA presentations began with C. Ganley, M.D.'s overview of the issues to be explored by the Committee. Efficacy data was reviewed by L. Goldkind, M.D. who concluded that the results of clinical trials followed predictions based on the PD properties of the compound: 1) no efficacy at acute treatment of episodic HB; 2) marginal, yet-to-be-properly-replicated efficacy at 1h prevention; and 3) optimal role in prevention of HB over time in the management of GERD (a new OTC indication) currently "a physician-diagnosed chronic disease requiring 4 to 8 weeks of therapy". L. Chin, M.D. described the Actual Use trials. A substantial number of patients used this medication for more than 24 days. After a detailed presentation of the main safety issues (the list is not exhaustive) related to very short (up to 10 days), short (up to 12 weeks) and long-term (several months and years) use of the drug, M. Avigan, M.D. raised the important consideration of whether omeprazole safety concerns actually can be addressed through labeling. The problem is that while the prescription use of the drug relies on "learned intermediary" (to evaluate patient and recognize and manage drug toxicity), OTC solely relies on labeling. From her review of the Label Comprehension data, K. Lechter, J.D., Ph.D. concluded that the AZ/PG data suggested potential for substantial use by persons who should consult a physician first; in addition, the sponsor had not listed the most recent label which differed from the tested label. L. Katz, M.D., M.P.H., Deputy Director, Division of OTC drugs, gave the charge to the Committee. The efficacy issues for discussion included the three indications for which approval was being sought and whether GERD is an acceptable OTC indication. The safety issues for discussion included short-term vs chronic intermittent use, safety concerns such as masking serious disease, potential for genotoxicity, tumorigenicity, and fetal developmental toxicity, rebound hyperacidity, hypergastrinemia, drug-drug interactions and discussions on the actual use and label comprehension issues.

#### **IX. Summary of NPDGIAC's Recommendations**

Recommendation regarding efficacy, safety, drug-drug interactions, actual use and labeled comprehension studies are summarized in Table 6. Voting results with regards to support for approval for OTC setting are summarized in Table 7.

**TABLE 6**  
**NDA 21-229**

**October 20, 2000 Advisory Committee's Recommendations on Efficacy, Safety, Drug-Drug Interactions, Actual USE and Labeled Comprehension Studies**

| A. EFFICACY                                                                                                                                                                                                                  |                                                                                                                                                                                     |                              |         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------|
| Indication, Study No.                                                                                                                                                                                                        | NO                                                                                                                                                                                  | YES                          | ABSTAIN |
| <b>Primary Efficacy Endpoint</b><br>1. Treatment of acute, occasional heartburn, acid indigestion or sour stomach<br>• Studies #092 and 095<br>• Occurrence of sustained complete relief of the first treated episode of HB. | "Based on the primary measure of efficacy is there a clinically significant improvement of acute symptomatic HB in either the 10 or 20-mg OME-Mg group compared to PL?"             |                              |         |
|                                                                                                                                                                                                                              | 13                                                                                                                                                                                  | 0                            | 1       |
| 2. Prevention of meal-induced heartburn symptoms if ingested at specified times prior to a meal.<br>• Studies 005 and 006<br>• Percentage of subjects HB-free over the entire 4-h period after a provocative meal.           | "Based on the primary measure of efficacy, is there a clinically significant improvement of HB symptoms in either the 10 or 20 mg OME-Mg groups compared to PL?"                    |                              |         |
|                                                                                                                                                                                                                              | 13                                                                                                                                                                                  | 1                            | 0       |
| There was consensus that the secondary efficacy analyses added some consistency in favor of the drug.                                                                                                                        |                                                                                                                                                                                     |                              |         |
| 3. 24-h prevention of heartburn<br>• Studies #171 and #183<br>• Complete prevention of HB between the first two doses of therapy                                                                                             | "Is there a clinically significant improvement of HB symptoms in either the 10 or 20 mg OME-Mg groups compared to PL?"                                                              |                              |         |
|                                                                                                                                                                                                                              | 14                                                                                                                                                                                  | 0                            | 0       |
| There was consensus that the secondary efficacy analyses added some consistency in favor of the drug.                                                                                                                        |                                                                                                                                                                                     |                              |         |
| B. SAFETY                                                                                                                                                                                                                    |                                                                                                                                                                                     |                              |         |
| Types and frequency of AEs reported in the clinical trials and in the post-marketing AE database                                                                                                                             | "Are there safety concerns for the OTC marketing of OME-Mg able to be addressed solely in labeling (identify risks) to consumers for a) short-term or b) chronic intermittent use?" |                              |         |
| When considering the questions raised by the FDA reviewer regarding:                                                                                                                                                         | Cannot do it in the Labeling                                                                                                                                                        | Can do it in the Labeling    | Abstain |
| 1) the masking of serious disease                                                                                                                                                                                            | 7                                                                                                                                                                                   | 5                            | 2       |
| 2) the potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity                                                                                                                                      |                                                                                                                                                                                     |                              |         |
| 3) rebound hyperacidity reported in the literature with discontinuation of therapy, and                                                                                                                                      | 8                                                                                                                                                                                   | 5                            | 1       |
| 4) hypergastrinemia that may be associated with the chronic or chronic intermittent use of omeprazole                                                                                                                        | (safety can be addressed)                                                                                                                                                           | (safety cannot be addressed) |         |
| C. DRUG-DRUG INTERACTIONS                                                                                                                                                                                                    |                                                                                                                                                                                     |                              |         |
| No vote was taken on the question "Are there drug-drug interactions that affect acceptability of OTC marketing of OME-Mg?"                                                                                                   |                                                                                                                                                                                     |                              |         |
| D. ACTUAL USE STUDIES                                                                                                                                                                                                        |                                                                                                                                                                                     |                              |         |
|                                                                                                                                                                                                                              | "Do these results suggest that OME-Mg will likely be used by consumers on a chronic basis for conditions other than episodic HB (e.g. GERD)?"                                       |                              |         |
| The chair altered the question by adding the clause on common HB to the question.                                                                                                                                            |                                                                                                                                                                                     |                              |         |
|                                                                                                                                                                                                                              | "Is the treatment of common HB as well as GERD an acceptable OTC indication?"                                                                                                       |                              |         |
|                                                                                                                                                                                                                              | 6<br>(Not acceptable OTC)                                                                                                                                                           | 7<br>(Acceptable OTC)        | 1       |

APPEARS THIS WAY  
ON ORIGINAL

| E. LABEL COMPREHENSION STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Factors to be considered in responding:</p> <ul style="list-style-type: none"> <li>a) The ability of consumers to appropriately self-select.</li> <li>b) The ability of consumers to use the correct dosage and for the period of time specified in the label.</li> <li>c) The ability of consumers to identify when they should see a physician before using the product and once they have begun using the product.</li> <li>d) The ability of consumers to identify serious adverse events.</li> <li>e) The ability of consumers to avoid interacting drugs.</li> <li>f) Use in women of childbearing age or in the pediatric population.</li> </ul> | <p>There was no vote on the question "Based on the results of the actual use and label comprehension studies, has the sponsor presented adequate data to substantiate that consumers will be able to use omeprazole appropriately in the OTC setting for: 1) acute symptomatic treatment, 2) prevention for up to 10 days.:"</p> <p style="text-align: center;">APPEARANCE<br/>ON ORIGINAL</p> |

**TABLE 7**  
**NDA 21-229**

**October 20, 2000 Advisory Committee's Recommendations on the Risk-Benefit (Approval) Question**

| Indication                                                                                                                                                                              | NO <sup>a</sup> | YES <sup>b</sup> | ABSTAIN |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------|---------|
| <b>A. OME-Mg 10 mg</b>                                                                                                                                                                  |                 |                  |         |
| ● Acute Symptomatic HB                                                                                                                                                                  | 11              | 2                | 0       |
| ● Prevention of Episodic HB                                                                                                                                                             | 10              | 2                | 1       |
| ● Treatment of Chronic HB                                                                                                                                                               | 9               | 3                | 1       |
| <b>B. OME-Mg 20 mg</b>                                                                                                                                                                  |                 |                  |         |
| ● Acute Symptomatic HB                                                                                                                                                                  | 11              | 2                | 0       |
| ● Prevention of Episodic HB                                                                                                                                                             | 10              | 2                | 1       |
| ● Treatment of Chronic HB                                                                                                                                                               | 9               | 3                | 1       |
| <p>a) NO means that there is no evidence of demonstration of efficacy/safety</p> <p>b) YES means that the risk/benefit ratio is acceptable for the OTC setting to support approval.</p> |                 |                  |         |

**X. OTC GERD: Opportunities and Constraints**

The sponsor has requested a treatment claim for the indication of acute episodic (occasional) heartburn, the symptom, based on studies 092 and 095, as well as a prevention claim based on studies 005 and 006. As summarized in Section IX of this review, based on the primary efficacy measure, no clinically significant improvement of HB symptoms was demonstrated in either the treatment or the prevention studies. These results were not unexpected because the drugs approved for these indications have pharmacodynamic properties that are very different to those of OME-Mg, a PPI. Their safety profile, together with rapid onset of action and short duration of

antisecretory effects, makes H<sub>2</sub>-receptor antagonists (and antacids) suitable for OTC use. On the other hand, the PD properties of OME-Mg, a PPI, are such that the onset of antisecretory effect is not rapid. However, upon repeated daily administration, these PD effects are long-lasting. The efficacy demonstrated in studies 171 and 183 and the results of Actual Use and Label Comprehension studies strongly suggest that the sponsor

This is a very different indication for which antacids and H<sub>2</sub>-receptor antagonists have been approved. Because of these considerations the members of the AC Committee were asked to openly discuss GERD. The Agency sought the input of experts in this field, Drs. Schuster, Cohen, Robinson and Sachs who agreed with Dr. Castell's recommendation that OME-Mg is suitable for the OTC management of HB. Other members of the AC committee, however, did not entirely agree with this recommendation (see Section IX of this review for voting results). **There are many aspects of OME-Mg efficacy that are not entirely clear.** Also in need of further clarification are some aspects of OME-Mg safety, especially those related to **inevitable long-term use.** These lingering concerns were clearly articulated in this safety presentation to the AC. Nearly half of the voting participants at that meeting thought that these safety concerns for the OTC marketing of OME-Mg cannot be addressed solely in labeling to consumers.

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**XI. Appropriateness of OTC Omeprazole**

There are two key sections in the CFR that follow directly from the statute (FD&C Act):  
330.10(3)(vi): "A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs."

At this time, many efficacy and safety issues regarding OTC omeprazole remain unclear. These include an answer to the questions of 1) whether it can be adequately labeled<sup>13</sup>; 2) does the use

---

<sup>13</sup> 330.10(v) "Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them unlikely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use."

of the product require professional supervision?; 3) does the treatment of \_\_\_\_\_ (the condition), whether symptomatic \_\_\_\_\_ or erosive esophagitis, require professional supervision?; and 4) the impracticability of treating \_\_\_\_\_ short-term.

Additional constraints to the availability of omeprazole OTC, as addressed by Dr. Karen Lechter (DDMAC), are summarized below.

- If the product is to be used **exclusively for prevention**,
  - There is no evidence that consumers will understand the appropriate indication.
  - It is not known if they would use the product appropriately.
  - It is not known if they can distinguish this product from other OTC products for relief.
- If the product is to be used **exclusively for prevention**, there is a need to ensure that consumers understand there is a delay in onset of action.
- The label comprehension studies suggested that substantial proportions of consumers who should check with a doctor before use may not do so. Evidence is needed that the consumer will check with a physician.
- It is not known if the current revisions to the label or if future revisions are understandable to consumers.

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9) tumorigenic potential of drug-induced hypergastrinemia, and 10), exaggerated rebound of gastric acid secretion and recurrence of esophageal lesions upon drug discontinuation.

Further discussion of these various issues is recommended. Participants to this scientific/regulatory approach should be representatives from several FDA Divisions, the sponsor, and key consultants. An additional AC meeting may need to be convened.

The goal of the proposed approach is to establish benchmarks on which to base the most appropriate regulatory action.

*October 31, 2000*

[ *ISI* ]

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:

NDA 21-229

HFD-180

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-181/MWalsh

HFD-180/JChoudary

HFD-180/LZhou

HFD-560/LChin

HFD-520/BVShetty

HFD-560/DKeravich

HFD-715/TPermett

HFD-715/Biopharm

HFD-021/STitus/AC

HFD-021/TPerez/AC

r/d 10.27/00 jgw

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Walsh

NDA 21-229

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

Dear Dr. Kozarek:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Chemistry section of your submission and have identified deficiencies in a Drug Master File (DMF) for the drug product. We are hereby notifying you that a deficiency letter, dated October 5, 2000, has been issued to \_\_\_\_\_ for DMF \_\_\_\_\_.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

[ \_\_\_\_\_ ]  
Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal and Coagulation Drug  
Products, (HFD-180)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

cc:  
Archival NDA 21-229  
HFD-180/Div. Files  
HFD-180/M. Walsh  
HFD-180/Reviewers and Team Leaders  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

Drafted by: M. Walsh 10/11/00  
Initialed by: L. Zhou 10/11/00  
final: M. Walsh 10/16/00  
filename: 21229.October-2000.AD.doc

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Walsh

Food and Drug Administration  
Rockville MD 20857

OCT 11 2000

[ ]

Dear \_\_\_\_\_

Between May 30 and June 7, 2000, Ms. Patricia S. Smith, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 1998006) of the investigational drug, Prilosec (omeprazole magnesium), performed for Procter & Gamble Co. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Smith presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. Protocol deviations:
  - a. Subject # 028192 was considered qualified to be enrolled in the study, but did not meet the protocol inclusion criteria.
  - b. At least 8 subjects (# 028210, 028204, 028212, 028199, 028200, 028201, 028202, and 028207) were included in the study although they did not complete the 7 day diary data required by the protocol in the screening period between Visit 1 and Visit 2.
2. Inadequate/inaccurate case histories. We note several discrepancies between source documents and case report forms, or between entries in the same case report.
  - a. Subjects # 028007, 028038, and 028039 were reported as "withdrew their consents" yet their CRFs report that they later completed the study.
  - b. Subject # 028070 CRFs show an entry on one page of Visit 2 that the subject had participated in a previous omeprazole magnesium study, and in another page of the same visit, the subject is shown as not participating in a previous omeprazole magnesium study.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Smith during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[ *SM* ]

John R. Martin, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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CFN: \_\_\_\_\_

Field Classification: VAI

Headquarters Classification:

- \_\_\_\_\_ 1) NAI
- X   2) VAI- no response required
- \_\_\_\_\_ 3) VAI- response requested
- \_\_\_\_\_ 4) OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

- \_\_\_\_\_ inadequate informed consent
- \_\_\_\_\_ inadequate drug accountability
- X   failure to adhere to protocol
- X   inadequate records
- \_\_\_\_\_ failure to report ADRS

cc:

- HFA-224
- HFD-180 Doc.Rm. NDA# 21-229
- HFD-180 Review Div.Dir. Talarico
- HFD-180 MO Avigan
- HFD-180 PM Walsh
- HFD-45 Reading File
- HFD-46 Chron File
- HFD-46 GCP/CIB File # 10126
- HFD-46 GCP/CIB Reviewer Malek
- HFD-46 CSO Huff
- HFR-SE450 DIB Debo
- HFR-SE450 Bimo Monitor Asente
- HFR-SE450 Field Investigator Smith
- r/d:KM:8/14/00
- reviewed:JRM:9/7/00
- f/t:jau:10/6/00
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**Note to Rev. Div. M.O.**

The field investigator reviewed the source documents of 85 subjects out of 212 enrolled. The inspection revealed few protocol violations and some inaccurate records that would not affect the reliability or integrity of the data. The data appear acceptable for use in support of the NDA.

TO: Mary Dempsey, Project Manager ([dempsey@cder.fda.gov](mailto:dempsey@cder.fda.gov))  
 Food and Drug Administration

FROM: Lewis B. Holmes, M.D.  
 Genetics & Teratology Unit, Pediatric Service  
 Massachusetts General Hospital, Boston, MA 02114

CC: Evelyn M. Rodriguez, M.D., M.P.H.  
 Dr. Mary Willy

RE: Analysis of 20 adverse event reports concerning exposure to omeprazole during pregnancy

DATE: September 11, 2000

These are the 20 reports I was asked to evaluate, which I have outlined as to period of exposure and phenotype. I have listed them chronologically, by date of the infant's birth:

| <u>Report Number</u> | <u>Infant DOB</u> | <u>Date of Report</u> | <u>Exposure to Omeprazole</u>       | <u>Phenotype of Infant</u>                        | <u>Significant Other</u>                       |
|----------------------|-------------------|-----------------------|-------------------------------------|---------------------------------------------------|------------------------------------------------|
| 1.<br>WAES92050713   |                   | 12-18-92              | 8d., starting at about 3.5 wks GA   | "mild random Duane's syndrome                     |                                                |
| 2.<br>WAES92060147   |                   | 9-11-92               | 18, wks to 32 wks GA                | Hydranencephaly; severe microcephaly; contracture | Mother was Class C Insulin-dependent diabetic  |
| 3.<br>19950900045    |                   | 9-21-95               | 2-91 (presumably treated one month) | Severely handicapped infant                       | Infant has 2 complex chromosome rearrangements |

|                    |          |                                                   |                                                                                                   |                                                                                                       |
|--------------------|----------|---------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| 4.<br>WAES93030842 | 6-10-93  | 7 d.<br>postconception<br>throughout<br>pregnancy | Sacral<br>lipomeningocele;<br>cleft lip and palate                                                |                                                                                                       |
| 5.<br>WAES93061143 | 7-8-93   | From conception<br>to 8 weeks GA                  | Anencephaly                                                                                       |                                                                                                       |
| 6.<br>19940700090  | 11-15-94 | From week 6 to<br>13 GA                           | Anencephaly                                                                                       |                                                                                                       |
| 7.<br>19940900104  | 10-3-94  | Approximately 6<br>to 13 weeks GA                 | products of<br>conception removed<br>at 13 weeks GA;<br>noted to have<br>"stopped<br>development" |                                                                                                       |
| 8.<br>19950200046  | 8-22-95  | First 4 weeks<br>postfertilization                | "hypoplastic heart"<br>(fatal)                                                                    |                                                                                                       |
| 9.<br>19951100030  | 11-17-95 | 30 wk GA to<br>delivery                           | Pyloric stenosis                                                                                  |                                                                                                       |
| 10.<br>19951200114 | 12-27-95 | Not clear                                         | Anencephaly                                                                                       | Positive family<br>history for<br>anencephaly and<br>spina bifida                                     |
| 11.<br>19950600134 | 11-13-95 | Last 3 months of<br>pregnancy                     | Severe<br>hypoglycemia and<br>metabolic acidosis<br>(no malformations<br>described)               |                                                                                                       |
| 12.<br>19950900177 | 11-6-95  | Not clear                                         | Cleft palate                                                                                      |                                                                                                       |
| 13.<br>19951000273 | 11-7-95  | ? presumably<br>first trimester                   | Anencephaly                                                                                       | Published case<br>reports; 2 births<br>to a woman<br>presumably<br>taking<br>omeprazole<br>throughout |
| 14.<br>19951000270 | 11-7-95  | ? presumably<br>first trimester                   | Severe talipes                                                                                    | Same mother as<br>case #13                                                                            |

|                    |          |                                               |                                                 |
|--------------------|----------|-----------------------------------------------|-------------------------------------------------|
| 15.<br>1996100099  | 10-22-96 | Part of first<br>month post-<br>fertilization | Small apical<br>ventricular septal<br>defect    |
| 16.<br>19990700200 | 7-23-99  | First trimester                               | Maxillary mono-<br>ostotic fibrous<br>dysplasia |
| 17.<br>19961000189 | 11-1-96  | Began —<br>(? First month)                    | "peromelia of left<br>arm"                      |

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|                    |       |          |                                                          |                                      |                                     |
|--------------------|-------|----------|----------------------------------------------------------|--------------------------------------|-------------------------------------|
| 18.<br>19971000103 | _____ | 12-4-97  | Until pregnancy diagnosed; then restarted 5-28-97        | Oculo-auriculo-fronto-nasal syndrome |                                     |
| 19.<br>B0049396    | _____ | 10-22-97 | First 8 weeks of gestation and from 21 weeks to delivery | "severe facial dysmorphism"          |                                     |
| 20.<br>19990100157 | _____ | 8-4-99   | First trimester                                          | Anophthalmia and hydrops             | Mother had surgery to treat obesity |

These are a very diverse group of outcomes. In considering whether any could have been caused by the exposure to omeprazole, I would add these qualifying comments for several of these cases:

1. "Mild, random Duane's syndrome". The Duane anomaly is a congenital eye movement disorder characterized by limitation in abduction and narrowing of the palpebral fissures. This has been identified as an effect of thalidomide, but not as an isolated finding. This type of outcome is not identified in newborn infants, as it is established only by a careful exam that requires the person's cooperation in following directions. It is not clear from the report that the finding persisted into childhood. I would not list this outcome as a major malformation.
2. The teratogenicity of maternal diabetes is known to produce a diverse group of major malformations. While some rare malformations are much more common in infants of diabetic mothers (IDM), there is no recognizable syndrome in many malformed IDM in contrast to infants affected by other maternal disorders that are teratogenic, e.g. maternal myasthenia or excessive alcohol consumption.
3. The report does not describe a specific phenotype and suggests that this infant had either a significant excess or deficiency (or both) of chromosome material. Chromosome abnormalities in the fetus have not been shown to have been produced by exposure to medication taken by the mother during pregnancy.
5. Pyloric stenosis is not a major malformation. It is caused by hypertrophy of muscle. While it has been tabulated in many epidemiologic studies as a "malformation", it is not a structural abnormality.
7. This fetus with anencephaly was exposed to omeprazole from weeks 6 to 13 of gestation, which would have been after a neural tube defect would have been visible (fourth week post fertilization).

8. This outcome is an elective termination of what would have been a spontaneous abortion. This can only be put in the context of spontaneous abortions which occur in about 15% of pregnancies. Since half of all spontaneous abortions are associated with a chromosome abnormality, it is unfortunate that the results of such studies were not provided.
9. Presumably the term "hypoplastic heart" refers to "hypoplastic left heart" or "hypoplastic right heart", both of which are observed regularly in malformations surveillance.
11. "Severe hypoglycemia and metabolic acidosis" are not part of the spectrum of outcomes included in the definition of major malformations that I use in evaluating the effects of human teratogens.
15. Ventricular septal defects are the most common type of heart defects. As described, we do not know if this is a muscular type or a membranous type. The muscular type closes spontaneously. It is so common that it is not being considered a major malformation by the National Birth Defects Prevention Study, a CDC-funded eight state study of the causes of selected major malformations identified from the surveillance of newborn infants.
16. "Maxillary mono-ostolic fibrous dysplasia" is an unusual outcome. Further information would be useful. Is there another name for this infant's condition?
19. "Severe facial dysmorphism" is a non-specific term, which could refer to either malformations or deformations or both. More information would be very helpful.
20. One consequence of surgical treatment of obesity is vitamin deficiency. This has been suggested to be a risk factor in case reports of neural tube defects, but not in infants with anophthalmia to my knowledge.

#### Evaluation of reports:

In carrying out a review of outcomes like these it would be helpful to have inclusion and exclusion criteria for what is considered a significant "abnormality". Clearly human teratogens can produce a wide spectrum of phenotypic effects. The focus on the occurrence of major malformations is usually used as these are a known effect of many teratogens. Furthermore, these findings can be put in the context of what occurs in the general, unexposed population, with the question: does this occur spontaneously? Is there anything distinctive about this infant's phenotype? When outcomes other than major malformations are considered potential teratogenic effects, the reviewer needs a reference point to its frequency in the unexposed population.

Experience has shown that case reports, such as adverse event reports, cannot establish causality (ref. 1). However, one can ask whether the outcomes reported show phenotypes that are "atypical" or distinctive, as teratogenic drugs often produce recognizable patterns of major and minor anomalies.

Since inclusion/exclusion criteria were not provided for this review, I have used my own (ref. 2). I have used these in determining the frequency of major malformations in the surveillance of major malformations in a consecutive population of 200,000 newborn infants (ref. 3). We are also using these criteria in the North American AED (antiepileptic drug) Pregnancy Registry in which the teratogenic potential of all AED used in pregnancy are being evaluated.

I have drawn these conclusions for my review of these 20 reports:

1. I cannot consider any of the cases reported to be omeprazole-related. There is no known teratogenic effect of omeprazole. The outcomes reported reflect the types of malformations which occur spontaneously and illustrate the more severe end of the spectrum.
2. Several of these outcomes are not major malformations. In this group I include the infants with Duane's Syndrome, hypoglycemia and pyloric stenosis.
3. One outcome was analogous to a spontaneous abortion, and not a newborn infant with birth defects.
4. Two infants had co-existing problems, specifically maternal insulin-dependent diabetes mellitus and a complex chromosome abnormality (not specified), which are more likely causes of the outcome described.
5. Almost all of the infants described had significant exposures to other drugs. While none reported is recognized as a human teratogen, they have not been studied well enough in human pregnancies to establish their apparent safety.
6. Ideally one could assess the dose and period of exposure, but the information presented on this small number of cases is too limited and does not include a wide range of doses. However, it was noted appropriately that the exposure in one pregnancy occurred after the malformation (anencephaly) would have been present in the exposed embryo/fetus.

#### References:

1. Shepard TH. "Proof" of human teratogenicity. *Teratology* 50:97-98, 1984.

2. Holmes LB. Need for inclusion and exclusion criteria for the structural abnormalities recorded in children born from exposed pregnancies. *Teratology* 59:1-2, 1999.
3. Nelson K, Holmes LB: Malformations due to presumed spontaneous mutations in newborn infants. *N Engl J Med* 320:19-23, 1989.

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Walsh

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** September 7, 2000  
**Time:** 2:30 p.m. - 3:00 p.m.  
**Location:** Corporate Building, Conference Room S200B

**Application:** NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

**Type of Meeting:** Discussion of issues for the upcoming Joint Advisory Committee Meeting

**Meeting Chair:** Charles Ganley, M.D., Director, HFD-560

**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### FDA Attendees:

#### Division of Over-The-Counter Drug Products. HFD-560

Charles Ganley, M.D., Director  
Linda Katz, M.D., Deputy Director

#### Division of Gastrointestinal and Coagulation Drug Products. HFD-180

Lilia Talarico, M.D., Director  
Steven Aurecchia, M.D., Deputy Director  
Hugo Gallo-Torres, M.D., Ph.D., GI Clinical Team Leader  
Mark Avigan, M.D., Medical Officer  
Scheldon Kress, M.D., Medical Officer  
Maria R. Walsh, M.S., Regulatory Project Manager

#### Division of Anti-Inflammatory, Analgesic, and Ophthalmological Drug Products. HFD-550

Lawrence Goldkind, M.D., Clinical Team Leader (Medical Reviewer for this application)

### Sponsor Attendees:

#### The Proctor and Gamble Company

Doug Bierer, Ph.D., Director, Regulatory Affairs  
Nora Zorich, M.D., Ph.D., Director, New Drug Development  
Keith Triebwasser, Ph.D., Manager, External Relations, Regulatory Affairs  
Tim Balm, Research Fellow, Clinical  
Linda C. Jones, Regulatory Affairs

#### AstraZeneca LP

Gary P. Horowitz, Ph.D., Executive Director, Regulatory Affairs

**Background:** AstraZeneca (sponsor) together with The Proctor and Gamble Co. (agent) submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets on January 27, 2000 for the following over-the-counter indications: 1) relief of heartburn, acid indigestion, and sour stomach; and 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food

and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise. This NDA will be discussed at a Joint Non-Prescription Drugs/Gastrointestinal Drugs Advisory Committee Meeting on October 20, 2000. The sponsor submitted a draft outline of their Advisory Committee Background Package, dated August 18, 2000, to the Division of Gastrointestinal and Coagulation Drug Products and requested feedback regarding the Agency's thinking/position on topics such as indications, dose levels, warnings, and specific safety topics in order to focus their presentation to the Joint Advisory Committee.

**Meeting:**

The Agency advised the sponsor/agent to focus on the following efficacy and safety issues in their presentation to the Joint Advisory Committee.

Efficacy

1. Treatment of heartburn: The data submitted are not sufficient to support an indication for acute symptomatic treatment of heartburn. The sponsor should explain why they believe the data supports the proposed indication.
2. Prevention of heartburn: The data submitted to support the proposed indication for prevention of symptoms for 24 hours moves from acute treatment of episodic heartburn to chronic use in consumers with gastroesophageal reflux disease (GERD). In the context of the Prilosec data, the Agency will ask the Committee to consider whether treatment of GERD is an appropriate OTC indication. If it is considered appropriate, the Agency may discuss other issues that will need to be addressed (e.g. revise label to accommodate a longer treatment period; include all comers in the actual use studies, etc.).

The sponsor/agent said they have additional data relevant to the actual use studies in patients who used the drug for over 10 days (i.e. why they exceeded the recommended duration). The Agency said the sponsor may present any data that has already been submitted to the Agency.

Safety

1. Specific adverse events: Focus on anaphylaxis, angioedema, hepatic injuries, visual abnormalities, and drug-drug interactions. Give overview of all other events.
2. Genotoxic/tumorigenic potential.
3. Hypergastrinemia effects, atrophic gastritis, and intestinal metaplasia.
4. Pediatric use: Specify the data used to support use in the 18 year old age group.

5. Rebound phenomenon.
6. Masking of serious disease.
7. Justification for proposed dose.

Safety should be addressed from two perspectives: 1) adverse events associated with short-term use; and 2) potential risks associated with long-term use or intermittent repeated use over time due to the nature of the target population and the pharmacodynamic properties of the drug.

The sponsor/agent asked if the Pregnancy Category of the prescription omeprazole formulation will be a topic for discussion since they wish to delete the warning statement. \_\_\_\_\_ in the proposed label. The Agency replied that this issue is still under review in a supplemental application.

Additional/Miscellaneous Issues:

The sponsor/agent clarified that Prilosec (omeprazole magnesium) Tablets are marketed OTC in Sweden (10 and 20 mg doses) and that no additional studies were conducted to "switch" the drug from prescription to OTC status.

The sponsor/agent expressed concern about the first episode response in the heartburn treatment studies. Therefore, additional analyses have been carried out regarding heartburn incidences separated by 2-3 days and the duration of the carry-over effect. These analyses will be officially submitted to NDA 21-229 today. An overview of the analyses was presented by the sponsor/agent (see attached slides). The Agency advised the sponsor not to include these analyses in their Advisory Committee Background Package as they are misleading.

Minutes Preparer: [ 151 ] 9/27/00

Chair Concurrence: [ 151 ] 9/27/00

Attachments/Handouts: Sponsor's Slides

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Meeting Minutes

Page 4

cc: Original NDA 21-229  
HFD-180/Div. Files  
HFD-180/Meeting Minutes files  
HFD-180/PM/M. Walsh  
HFD-180/H.Gallo-Torres  
S.Aurecchia  
L.Talarico  
HFD-560/PM/D.Keravich  
HFD-560/L.Katz  
C.Ganley

Drafted by: M.Walsh 9/13/00  
Initialed by: H.Gallo-Torres 9/13/00  
S.Aurecchia 9/14/00  
L.Talarico 9/14/00  
L.Katz 9/20/00  
C.Ganley 9/24/00

final: M.Walsh 9/26/00  
filename: N21229.September-2000.minutes.doc

MEETING MINUTES

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Walsh

## MEMORANDUM OF TELECON

DATE: September 6, 2000

APPLICATION NUMBER: NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Linda C. Jones, Regulatory Affairs  
Phone: (513) 622-3176  
Representing: The Proctor and Gamble Company

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**SUBJECT:** Discrepancy in ISS Tables re: Fatal and Non-Fatal Events

**BACKGROUND:** AstraZeneca (sponsor) together with The Proctor and Gamble Co. (agent) submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets on January 27, 2000, for the following indications: 1) relief of heartburn, acid indigestion, and sour stomach; and 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise.

Per the medical reviewer, Dr. Sheldon Kress, I called Linda Jones on September 5, 2000 and left a voice mail requesting clarification regarding a discrepancy in the Integrated Summary of Safety (ISS). In section 8.3.3, "Prescription Omeprazole Clinical Trial Adverse Events," the data contained in Appendix 2, Table 31, "Worldwide Clinical Trial Serious Adverse Events with Fatal Outcome," match the data in Tables 42 and 43 for adverse events with non-fatal outcomes rather than the data contained in Tables 44 and 45 for adverse events with fatal outcomes.

**TODAY'S CALL:** Ms. Jones called me and said that the title of Table 31 is incorrect. The correct title should be, "Worldwide Clinical Trial Serious Adverse Events with Non-Fatal Outcome."

I thanked Ms. Jones for the clarification and the call was then concluded.

[ 151 ] 9/6/00

Maria R. Walsh, M.S.  
Regulatory Project Manager

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NDA 21-229

Page 2

cc: Original NDA 21-229

HFD-180/Div. File

HFD-180/M. Walsh

HFD-180/S.Kress

H.Gallo-Torres

Final: M. Walsh 9/6/00

filename: 21229.September-2000.telecon.doc

TELECON

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# Electronic Mail Message

Date: 9/6/00 2:57:39 PM  
From: Correa, Adolfo ( aic8@cdc.gov )  
To: Willy, Mary E. (FDA) ( WILLYM@A1 )  
To: Dempsey, Mary J. (FDA) ( DEMPSEYM@A1 )  
To: Rodriguez, Evelyn M. (FDA) ( RODRIGUEZE@A1 )  
Cc: Correa, Adolfo ( aic8@cdc.gov )  
Cc: Erickson, Dave ( jdel@cdc.gov )  
Subject: requested review of pregnancy-related outcomes

Attached please find the following:

- 1) Review of epi papers
- 2) Review of reports of adverse events with classification table (excel file)
- 3) Comments on cohort study

<<omeprazolepapers.doc>> <<fdacohort.doc>> <<adverse event reports.doc>>  
<<FDACASES2.xls>>

Please let me know if you have any questions.

Thank you for the opportunity to assist you with this interesting and important problem.

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## Review of Epidemiological Studies on Omeprazole and Pregnancy Outcomes

1. Källén B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. *Brit J Obstet and Gynaecol* 1998;105:877-81.

### 1.1. Summary

This study examined the relation between use of acid-suppressing drugs early in pregnancy and risk of congenital malformations using a retrospective cohort design. The study population consisted of offspring to Swedish pregnant women born between 1995 and early 1997 ( $n \sim 200,000$ ). The main source of data was the Swedish Medical Birth Registry, which consists of a database of computerized records on antenatal care and other prenatal factors (e.g., smoking and drug use), delivery records, and pediatric examinations of all newborns, collected prospectively in a standardized format. This registry was the source of the study cohort (mothers who had used any acid-suppressing drugs after becoming pregnant and before the first antenatal visit [1<sup>st</sup> trimester exposure]), data on drug use, and cases of congenital malformations. Another data source was the Registry of Congenital Malformations, which was linked to the Medical Birth Registry to ascertain additional cases. Data on drug use stored in this registry include information on proprietary name, dosage, and sometimes when the drug was used. Data on drug use, collected by interview by midwives at the time of the first antenatal clinic visit (1<sup>st</sup> trimester), were used to identify the study cohort: pregnant women who used proton-pump blockers ( $n=275$ ), H<sub>2</sub>-receptor antagonists ( $n=255$ ), or both types of drugs early in pregnancy ( $n=20$ ). Cases of malformations were infants in the Medical Birth Registry with conditions classified with an ICD9 code for congenital malformations or infants who had been reported to the Registry of Congenital Malformations. Cases were ascertained among stillbirths and in early postnatal life. Infants with cardiovascular defects were checked against a register of infants with congenital heart defects diagnosed in infancy. Congenital malformations diagnosed prenatally and resulting in pregnancy termination were excluded. Risk ratios estimates were based on observed to expected ratios (i.e., comparisons with all births in the Medical Birth Registry), stratified by year of birth, maternal age, parity, and smoking habits early in pregnancy. Comparisons between different drug groups and analysis of certain population characteristics were made with odds ratios (OR).

Compared to women in the general population, women using acid-suppressing drugs in early pregnancy in this cohort were more likely to be older, primiparous, and smokers. Among the cohort of 547 exposed pregnancies, there were 17 offspring with malformations identified in the Medical Birth Registry, for a crude prevalence rate of 3.1% (95% CI 1.8-4.9), compared to a crude rate of 3.9% among all infants. The OR for congenital malformations in the drug exposed infants compared to all infants in the registry stratified by year of birth, maternal age, parity, and maternal smoking early in pregnancy was 0.72 (95% CI 0.41-1.24). The corresponding OR for infants after only proton-pump blocker use was 0.91 (95% CI 0.45-1.84), after only H<sub>2</sub>-receptor antagonists use 0.46 (95% CI 0.17-1.20), and after omeprazole use 0.59 (95% CI 0.28-1.25). The authors report that there was no difference in the total proportion of malformations among the five groups (omeprazole, lansoprazole, cimetidine, ranitidine, and omeprazole and ranitidine combined) but provide no data on the denominators for these five groups.

Many of the malformations were minor. In the proton pump blocker group, there were six infants with congenital heart defects (three VSD, one ASD, one PDA in a term baby, one unspecified), one with urethral valve, one with undescended testis, one with an unspecified facial anomaly, and one with Down's syndrome. In the H<sub>2</sub>-receptor antagonist group there was one infant with a cardiovascular defect (unspecified), one with unilateral hydronephrosis diagnosed prenatally, one with a non-immune hydrops, one with a cerebral arterio-venous malformation, one with undescended testis, one with an

unstable hip, and one with hypospadias. In the group who used both omeprazole and ranitidine, there was one case of hypospadias.

The authors conclude that, although a teratogenic effect of these drugs cannot be ruled out, the individual risk after exposures during the first trimester seems negligible.

## 1.2. Strengths and Limitations

### 1.2.1. Strengths

The cohort design allowed an independent assessment of both exposure and outcome, minimizing the potential for systematic errors on exposure and outcome classification. Since this study was based on the Medical Birth Register, there were no refusals to participate, minimizing the potential for selection bias. Drug use data were collected prospectively, in a standardized manner, and included information on drug use during the first trimester, the period of higher susceptibility to the effects of teratogens for most organ systems. This allowed identification of well-defined and mutually exclusive exposure groups. Statistical analysis took into account year of birth, maternal age, parity and smoking habits. This helped minimize potential confounding by these variables. Finally, the authors acknowledge that the size of the study does not allow the exclusion of an increased risk of teratogenicity from omeprazole for specific defects.

### 1.2.2. Limitations

One limitation of this retrospective cohort is that the Medical Birth Register, which served as the source of this cohort, had no information on spontaneous abortions. This study, therefore, could not rule out an effect of omeprazole on spontaneous abortions.

The authors provide no information on the proportion of exposed pregnancies that may have had prenatal ultrasound, the proportion of pregnancies with prenatally diagnosed cases of malformations, or the proportion of such pregnancies that were terminated. The absence or low frequency of some of the more common major malformations (e.g., anencephaly, Down's syndrome, gastrointestinal anomalies) in a cohort of high risk women, suggests that prenatal detection and pregnancy termination may have occurred in this cohort. If prenatal diagnoses and pregnancy terminations occurred more frequently among women who used omeprazole early in pregnancy than among other groups of women, the rate of malformations among offspring to such women would be underestimated. This could well explain the lower rate of malformations in the study cohort compared to the rate of malformations in the Medical Birth Register and the low prevalence of major malformations in the study cohort. Therefore, it is difficult to exclude the possibility that the results are an artifact of selective pregnancy terminations in the exposed group.

The authors provide limited information on the completeness of ascertainment of cases of malformations in the Medical Birth Register. A recent publication based on data from the same Medical Birth Register (Wennerholm et al, Incidence of congenital malformations in children born after ICSI. *Human Reproduction*, 2000;15:944-8) suggests that this register may miss up to a third of the malformations subsequently found in the Register of Congenital Malformations. This under ascertainment could explain the low prevalence of

major malformations in this cohort. The lack of information on the basis of the diagnoses of congenital malformations makes it difficult to assess the accuracy of the diagnoses, and of the classification of cases in this study. The fact that the cases of ventricular septal defects had not been evaluated at the Child Cardiology Register suggests that such cases might have been mild and that the classification of cases was subject to error. Errors in the classification of cases as non-cases and of non-cases as cases may have attenuated differences in rates of malformations between the comparison groups.

Inclusion of ill-defined conditions and minor anomalies as outcomes increased the sample size but may have been counterproductive. If omeprazole is associated with specific defects that originate in the first trimester, inclusion of infants with ill-defined conditions (e.g., facial anomaly, unspecified congenital heart defects) and of undescended testis and hypospadias in the analysis may have diluted any effects from exposure. Since hypospadias and descent of the testis do not occur until late in pregnancy, use of exposures that occur early in pregnancy may have resulted in misclassification of the more relevant exposures (i.e., late in pregnancy).

The authors provide no frequency distribution for congenital malformations in the reference population. In the absence of such a distribution, it is difficult to establish that the observed cases among the exposed are no different from the expected.

The reference group for estimation of odds ratios was not clearly defined. Did the reference group consist of all births in the Medical Birth Register? Or did it consist of the all births minus the study cohort? Use of the former reference group might have attenuated any effects from omeprazole.

One of the major limitations of this study is the size of the cohort. The study may have been of sufficient size to detect at least a moderate increase in the rate of all malformations in the cohort compared to all births (i.e., RR 1.65, power of 0.80,  $\alpha=0.05$ , 1-sided test). However, since exposure to most teratogens is likely to result in an increased risk of specific malformations rather than an increase in all malformations, this study may have lacked adequate power to rule out an increase in the risk of specific malformations from omeprazole use early in pregnancy.

## **2. Lalkin A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.**

### **2.1. Summary**

This cohort study examined whether omeprazole use during pregnancy was associated with an increased risk of malformations, spontaneous abortions, decreased birth weight, or perinatal complications. The study population consisted of pregnant women counseled early in pregnancy by one of four teratogen information centers: Motherisk (Toronto, Canada); Telefono Rosso (Rome, Italy); Service de Pharmaco-Toxicovigilance (Lyon, France), and Centro Regionale d'Informazione sul Farmaco (CRIF-Milan, Italy). At the initial consultation, such women were interviewed to elicit information on maternal demographic characteristics, medical and obstetric histories, indication for treatment and time of exposure, concurrent medications, and family history of birth defects. Shortly

after delivery, each woman was recontacted regarding pregnancy outcome, labor and delivery, and neonatal complications. Women exposed to omeprazole during pregnancy (n=113) were individually matched with two reference groups: pregnant women exposed to nonteratogenic drugs; and disease-paired controls who used histamine blockers for similar indications. Matching criteria were maternal age, smoking pattern, and alcohol consumption. The primary endpoint was the incidence of major malformations (i.e., those having an adverse effect on function or social acceptability). Secondary endpoints were pregnancy outcome, birth weight, rates of preterm delivery, and neonatal health problems.

Women from the four participating centers had similar reproductive, smoking and alcohol use characteristics. Exposure to omeprazole during the period of organogenesis (4-14 weeks of gestation) was reported by 89% of the mothers, and throughout gestation by 15 % of the mothers. Disease-paired controls reported fewer previous miscarriages than the nonteratogenesis controls. Women who used omeprazole during pregnancy were prescribed other agents more often than their disease-paired controls. The prevalence rates of major malformations in the omeprazole, disease-paired control, and nonteratogenic control groups were 4/78 (5.1%), 3/98 (3.1%), and 2/66 (3.0%), respectively. Among omeprazole exposed offspring, the major defects were ventricular septal defect (1), polycystic kidneys (1), ureteropelvic junction stenosis (1), and patent ductus arteriosus (1). Among disease-paired controls, the major defects were atrial septal defect (1), and ventricular septal defect (2). Among nonteratogenic controls, major defects were atrial septal defect (1) and developmental delay (1). The rates of spontaneous abortions in the omeprazole, disease-paired control, and nonteratogenic control groups were 16/113 (14%), 9/113 (8%), and 9/113 (8%), respectively. The rates of elective abortions in the omeprazole, disease-paired control, and nonteratogenic control groups were 6/113 (5%), 3/113 (3%), and 5/113 (4%), respectively. No differences were found for preterm delivery, mean birth weight, and gestational age at delivery or method of delivery. There were no differences in jaundice or the number of days in the intensive care unit between groups (data not shown). The authors conclude that there is no association between exposure to omeprazole and risk for major malformations, spontaneous abortions, decreased birth weight, or perinatal complications.

## 2.2. Strengths and Limitations

### 2.2.1. Strengths

The cohort design allowed ascertainment of various pregnancy outcomes and an independent assessment of both exposure and outcome, minimizing the potential for systematic errors on exposure and outcome classification. Although the study combined populations from four teratology information centers (Toronto, Rome, Milan, and Lyon), the four populations appeared to share similar reproductive and lifestyle characteristics (i.e., smoking and alcohol consumption habits). Drug use data were collected prospectively and included information on indication for treatment and time of exposure, concurrent medications, and family history of birth defects. Two reference groups were included in this study: one consisting of diseased-paired individuals and another of women who had taken drugs considered to be nonteratogenic. These reference groups were matched to the exposed group on selected potential confounders, including maternal age, maternal smoking and alcohol consumption habits. Another strength is the collection of data on and evaluation of several pregnancy outcomes. Lastly, the authors indicate the minimal excess risk for malformations and spontaneous abortions that their study can identify and acknowledge that their study does not have adequate power to detect a 3-fold increase in the rate of malformations.

### 2.2.2. Limitations

This study is based on a cohort of pregnant mothers counseled by teratogen information centers. This cohort includes mothers who took other medications other than omeprazole. However, this cohort does not include mothers who might have taken omeprazole but did not seek advice from the teratogen information services. Such a universe or reference population is not known and the period of births is not specified. Therefore, it is not possible to know how representative the cohort is of pregnant mothers who took omeprazole or any other medications during pregnancy. There is a possibility that pregnant women who took omeprazole during pregnancy and who might be more susceptible to adverse pregnancy outcomes from such exposures might have chosen not to call the participating centers for advice. From the information provided in the article, it is not possible to exclude this type of selection bias as a possible explanation for the study findings.

The authors provide no information on the calendar period of conception or birth for the subjects in this study. Although the exposed and reference groups are similar in maternal age, and alcohol and tobacco use, it is not clear that they are comparable on the year of birth and, therefore, on other potential confounders that might have varied over time, such as infections, diet, or use of multivitamin supplements.

Information on pregnancy outcome, labor and delivery, and neonatal complications was obtained from interviews of the mothers shortly after delivery. How successful this approach was in ascertaining all pregnancy outcomes, however, is unclear. Pregnancy losses early in pregnancy may go unrecognized, resulting in an underreporting of the true number of spontaneous abortions. Such underreporting could result in an underestimation of the rates of spontaneous abortions. The low rate of spontaneous abortions in the control groups (8% vs. an expected rate of at least 11%) suggests that underreporting of spontaneous abortions may have occurred in this study. If this kind of error occurred to the same extent in the exposed and reference groups, the power of the study to detect a difference in rates would be minimized. This may be one explanation for the findings on spontaneous abortions.

The definition and ascertainment of malformations were problematic. The study relied on a somewhat subjective definition of malformations (i.e., those having an adverse effect on either the function or social acceptability of the individual). This definition leaves a good deal of latitude for interpretation by those reporting the malformations, and may have resulted in a good deal of variation in reporting of malformations, with some malformations being underreported and some conditions being erroneously reported as malformations (e.g., developmental delay). In addition, interview data on the presence/absence of malformations and on the type of malformations can also be subject to error. Some malformations (e.g., some cardiac anomalies and syndromes) may be undiagnosed or misdiagnosed shortly after birth, particularly if assessments are not carried out with standardized methods. If nondifferential with respect to exposure group, such misclassification errors can result in attenuation of a difference in rates of malformations between study groups.

Although the authors provide information on the number of pregnancy losses in each comparison group, the authors provide no information on the proportion of pregnancies that

may have had prenatal ultrasound, the proportion of such pregnancies with prenatally diagnosed cases of malformations, or the proportion of pregnancies that were terminated due to the presence of a malformation. The authors provide information on the number of therapeutic abortions but not on the indications for such abortions or on whether the indications for such abortions were similar for the three comparison groups. If prenatal diagnoses and pregnancy terminations occurred more frequently among women who used omeprazole early in pregnancy than among other groups of women, the rate of malformations among offspring to such women would be underestimated.

The comparison groups were limited in size. The authors indicate that the incidence rate of malformation in the omeprazole group did not differ from the rates in the control groups. This is partly true. The rate of malformations was slightly higher in the omeprazole group than in either control group (RR = 1.67, 95% CI 0.15-48.67), but the confidence interval was wide and included the null value. The lack of a statistically significant difference may have reflected no difference in risks but it may have also been due to the low prevalence of malformations and the limited size of the cohort. The fact is that this study only had limited power (i.e., 7%) to detect a 61% increase in risk of malformations. For spontaneous abortions, the same issue applies. There was a higher rate of spontaneous abortions in the omeprazole group compared to either of the control groups (RR = 1.74%, 95% CI 0.66-6.02), but the confidence interval was wide and included the null value. Exclusion of the mothers with scleroderma and lupus from the omeprazole group reduces but does not nullify this difference in rates of spontaneous abortions (RR=1.48, 95% CI 0.49-5.43). If one compares the rates of any adverse outcome (i.e., spontaneous abortion, elective abortion or birth defect), one can observe that there is a 71% increased rate of such an outcome in the omeprazole group than in the disease-paired group (RR =1.71, 95% CI 0.85-4.04). Again, this increase is not statistically significant, but it is consistent for the two control groups. Conversely, the rate of live births is 8% lower in the omeprazole than in the no-teratogen control group (RR= 0.92, 95% CI 0.78-1.06). This difference is not statistically significant, but it is consistent for the two control groups. This study only had a 31% power to detect such a difference in live births.

The authors indicate that only a minority of the patients (15%) reported omeprazole use throughout pregnancy. However, in the analysis of preterm delivery, birth weight, gestational age and method of delivery, they seem to include in the denominator (n=113) all patients, not only those exposed throughout pregnancy. Such inclusion would result in classification of patients who were unexposed in the last trimester as exposed to omeprazole and in the attenuation of any difference in rates in prematurity, low birth weight, and other neonatal health problems between the exposed and control groups.

### **3. Ruigomez A, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. Am J Epidermal 1999;150:476-81.**

#### **3.1. Summary**

This study examined the relation between use of cimetidine, omeprazole, and ranitidine during the first trimester of pregnancy and prevalence of congenital malformations using a retrospective cohort design. Two computerized data sources were used to construct the study cohort: the United Kingdom

General Practice Research Database and the Italian Friuli-Venezia Giulia Health Database. The study cohort included pregnancies among women less than 45 years of age for the period 1991 to 1996: 1,179 from the United Kingdom, and 1,057 from Italy. After ascertainment of last menstrual period dates, the authors identified women who received a prescription for cimetidine, omeprazole, or ranitidine during the first trimester of pregnancy and a control group of pregnant women who had not received these drugs during the first trimester. Women with spontaneous, elective abortions, or ectopic pregnancies were excluded. Outcomes included stillbirths (pregnancy losses after 27 weeks of gestation and pregnancy terminations due to a prenatal diagnosis of malformations) and congenital malformations (live birth or still with a structural defect detected prenatally, at birth, or during the first year of life. In the UK database, the authors reviewed the records of all cases and requested additional medical record information when the information for classification was inadequate). In the Italian cohort, the authors reviewed medical and vital records for children admitted to the hospital during infancy with an ICD9 code for a congenital malformation. Birth defects known to be genetic were excluded.

There were 20 stillbirths, and 2,261 live-born babies in both cohorts combined, 100 offspring being identified with a malformation (68 in the UK group and 32 in the Italian group). The overall malformation rate was 4.4%. The rates of malformations in the cimetidine, omeprazole, ranitidine, and control groups in the combined cohort were 11/237 (4.6%), 5/139 (3.6%), 20/330 (6.1%), and 64/1575 (4.1%), respectively. The relative risks for cimetidine, omeprazole, and ranitidine in both cohorts combined were 1.2 (95% CI 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CCI: 0.8, 2.4), respectively, compared with the control group. No specific grouping in the distribution of malformations was observed in any of the three exposed groups. Moreover, no relation was found between drug exposure and preterm delivery or growth retardation. The findings of this study suggest that use of acid-suppressing drugs during the first trimester of pregnancy is not associated with a major teratogenic risk.

### 3.2. Strengths and Limitations

#### 3.2.1. Strengths

This study has the following strengths. The cohort design allowed an independent assessment of both exposure and outcome. This study was based on two different populations, in which there were computerized records of hospitalizations, births, and prescriptions, which allowed the construction of the study cohort and identification of outcomes. Drug use data were collected prospectively, and included information on drug use during the first trimester of pregnancy. Pregnancy terminations due to a prenatal diagnosis of a malformation were included in this evaluation. Ascertainment of cases of malformations was based on objective criteria (i.e., presence of an ICD9 code for a malformation in the database). In addition, there was an attempt to validate cases identified in the database in one of the two sub cohorts (Italian). Finally, the authors excluded infants with genetic syndromes, which would not be associated with drug exposure and would only dilute any effects from exposure.

#### 3.2.2. Limitations

Since this study excluded spontaneous abortions, the study could not rule out an effect of omeprazole (or the other acid-suppressing drugs) on spontaneous abortions.

The case definition in this study was based on ICD9 codes present in the databases.

However, the authors provide no information on the types of evaluations that the ICD9 codes were based on. There was an attempt to validate cases in one of the databases (Italian), but there is no information provided on the number of false positives or on the number of cases that had to be reclassified. Although misclassification of one case for another may have no impact on the between-group comparisons of overall rates of malformations, it may result in attenuation of differences in rates for specific malformations.

There was a difference in case ascertainment in the UK and Italian cohorts, which may explain the difference in prevalence in malformations in the two cohorts. It would have been interesting to see the impact of such differences in the types of cases that were ascertained. Unfortunately, data on malformations were not presented separately for the UK and the Italian cohorts.

The exposed groups were small in size, resulting in a limited power to detect an overall increased risk for congenital malformations. For the omeprazole group (n=139), the minimum overall increased risk for RR the study could detect was about 2.5 (1-tailed test). However, since exposure teratogens is likely to result in an increased risk of specific malformations rather than an overall increase in all malformations, this study probably lacked adequate power to rule out a 4-fold increase in risk for specific malformations whose prevalence is about 1 per 1000 or less (e.g., some specific heart defects). The limited sample size did not allow evaluation of potential confounders such as maternal age, family history of congenital anomalies, and use of multivitamins.

#### **4. Källén B. Use of Omeprazole during pregnancy – no hazards demonstrable.**

##### **1.1. Summary**

This retrospective cohort study is an extension of an earlier study based on the Swedish Medical Birth Registry (Källén B, 1998). The study population was expanded to include infants born between 1997-1999 to the cohort of infants born between 1995 and early 1997. This study also excluded pregnancies that resulted in spontaneous abortions and pregnancies that were terminated as a result of a prenatal diagnosis of a congenital malformation. A total of 955 infants exposed to Omeprazole were identified: 863 exposed in early pregnancy, and 131 later in pregnancy. Those exposed in early pregnancy included some exposed later in pregnancy, and vice versa. Outcomes studied include: congenital malformations, perinatal survival, low birth weight, and low Apgar scores, and hospitalization through 1997.

The rate of twinning was slightly lower among infants with earlier exposures compared to infants in the general population (2.3% vs. 3.1%). Similarly, the rate of malformations was slightly lower among infants with earlier exposures compared to infants in the general population (2.5% vs. 3.6%). Infants with earlier exposures had rates of perinatal mortality and low birth weight that were similar to infants in the general population, but the number of infants with these outcomes was small. This study identified 5 additional cases of malformations from the Medical Birth Registry among infants born in the period of extension (1997-1999). The odds ratio for having a malformed infant, stratified for year of birth, maternal age, parity, and maternal smoking was 0.82 (95% CI 0.50-1.34). There were eight infants with cardiac defects, seven of which were considered to be mild. The stratified odds ratio for any cardiovascular malformation was 1.9 (95% CI 0.8-4.4), and for VSD 1.7 (95% CI 0.5-3.9).

There was no evidence of an increased risk of low Apgar scores or of hospitalizations by the end of 1997 among infants who had been exposed to Omeprazole in pregnancy.

## 1.1. Strengths and limitations

### 4.2.1. Strengths

This study has the same strengths as the earlier study and, in addition, has the strength of including 371 (863-492) additional infants exposed early in pregnancies.

### 4.2.2. Limitations

This study has the same limitations as the earlier study: possible selection due to exclusion of spontaneous abortions and pregnancies terminated due to a prenatally detected malformations; and underascertainment and misclassification of cases after birth. The slightly lower rate of malformations among the exposed early in pregnancy compared to the rate in the general population would suggest that prenatal detection and pregnancy termination may have it made difficult, if not impossible, to see an excess risk from Omeprazole. The report does not make clear what proportion of the pregnancies classified as early exposures had late exposures and vice versa. Without a better clarification of the classification of exposure, more information on the rates of spontaneous abortions on the exposed and unexposed, the rates of pregnancy terminations in the exposed and unexposed, and some data on the frequency distribution of malformations in the exposed and unexposed, studies based on the Swedish Birth Register are not likely to provide a reliable answer to the question of whether Omeprazole is safe to use early in pregnancy. This study had limited power to rule moderate adverse effects on pregnancy outcomes from exposure to Omeprazole later in pregnancy.

## 5. Synthesis

These retrospective cohort studies provide no evidence for an increased risk of congenital malformations or other pregnancy outcomes in relation to omeprazole use during the first trimester of pregnancy. However, findings from these studies are difficult to interpret in light of several methodological issues, including: potential selection bias related to the exclusion of spontaneous abortions and pregnancy terminations due to prenatal diagnoses of congenital malformations; limitations in case definition, ascertainment, validation, and classification; potential confounding; and inadequate power to detect increased risks for specific malformations (e.g., cardiac septal defects) or other specific pregnancy outcomes.

Adolfo Correa, MD, PhD  
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9.05.00

APPEARS THIS WAY  
ON ORIGINAL

**Comments on the design characteristics and feasibility of a large, prospectively designed epidemiological study of women exposed to Omeprazole during pregnancy**

Since some of the issues of concern regarding use of Omeprazole during pregnancy relate to spontaneous abortion and congenital heart defects among offspring, desirable design characteristics of a prospective cohort study to address these issues include:

- Determination of the minimum excess risk that would be of clinical and public health importance to detect.
- Estimation of early pregnancy losses.
- Estimation of size of cohort study to detect the minimum excess risk for spontaneous abortions, and for malformations accounting for early pregnancy losses. The following numbers provide a rough idea of the kind of sample sizes needed per cohort of exposed and unexposed pregnancies to detect a minimum relative risk for one of the more common major congenital heart defects (i.e., ventricular septal defects) with a baseline prevalence of about 1 per 1000:

| Minimum RR | N per exposure group |
|------------|----------------------|
| 2          | 4300                 |
| 3          | 1500                 |
| 4          | 800                  |
| 5          | 560                  |

For other heart defects, with a much lower prevalence, the sample sizes would have to be much greater.

- Enrollment of a large cohort of women planning a pregnancy or who have just become pregnant.
- A substantial number of such women end up using Omeprazole during the first trimester of pregnancy.
- Baseline and regularly scheduled interviews and examinations of all women in the cohort are conducted to ascertain
  - Pregnancy status
  - Use of Omeprazole
  - Use of other prescription and nonprescription drugs
  - Use of alcohol and cigarette smoking

- Use of vitamin supplements
- Illnesses during the first trimester
  
- Follow-up of all women to ascertain, evaluate, and validate all pregnancy outcomes, using standardized procedures.
  
- Create and manage, on an ongoing basis, a complex database.
  
- Conduct timely evaluations of safety issues.

However, implementation of such a prospective cohort study of pregnant women exposed to Omeprazole, or to any other single drug, is likely to require extensive resources and be prohibitively costly and inefficient. An alternative and probably more efficient approach would be to develop and implement a protocol for post-marketing surveillance for a variety of drugs, prescription and nonprescription, using standardized methods and applying this to a large population base over an extended period of time. The infrastructure for this type of surveillance might be a network of centers likely to serve as a resource for information or prenatal care to large populations of women of reproductive age (e.g., major medical centers, HMOs). Such a post-marketing surveillance network would be able to develop and use standardized procedures to collect baseline and follow-up information on all participants, including information on drug exposure, and schedule follow-up contacts of participating women with obstetricians, pediatricians, and dysmorphologists and other specialists (e.g., clinical geneticists, pediatric cardiologists) at regular intervals, around the delivery dates, and during infancy. This monitoring system would also be able to carry out follow-up contacts at one year of age and to request medical records as needed. A data coordinating center for the network could be set up to collect and process the data, to implement quality assurance and control procedures, and to effectively manage such a complex database. Such a data coordinating center could be structured to conduct timely evaluations of trends of drug use among pregnant women, of safety questions about specific drugs or combinations of drugs in comparison to exposures that are less likely to have adverse effects on pregnancy outcome, and to conduct regular screening for potential adverse effects through nested case-control studies and case-crossover studies.

The above alternative approach will require extensive resources. It might be useful to come up with budget estimates for such a monitoring system, compare such budget estimates with the current total budget for all existing pregnancy drug registries, and evaluate the added value for the extra cost.

Adolfo Correa, MD, PhD  
09.05.00

APPEARS THIS WAY  
ON ORIGINAL

## Review of twenty adverse event reports in relation to exposure to Omeprazole

The twenty adverse event reports include:

- 18 reports of congenital birth defects or chromosomal disorders
- 1 report of a fetal death, and
- 1 report of hypoglycemia, respiratory distress and pneumonia.

Imputing any kind of probability of association of these reports to exposure to Omeprazole is subject to a great deal of uncertainty for several reasons. These reports come from different parts of the world over a period of several years and without sufficient information to assess the completeness and accuracy of such reports. The population at risk that gave rise to these cases is an ill-defined universe. Consequently, there is no way of estimating the rate of adverse events among exposed and unexposed pregnancies, and of determining the adverse events among exposed pregnancies represent more than the expected number of events.

Nonetheless, based on the limited information available in these reports, I classified the cases of birth defects into one of the following categories of association with in utero exposure to Omeprazole possible, unlikely, and unclear, using the following two criteria of temporal relation and alternative explanation:

Possible: if there was an indication that exposure to Omeprazole might have occurred during the first trimester of pregnancy.

Unlikely: if there was little indication of exposure to Omeprazole during the first trimester of pregnancy or if there was a strong alternative explanation for the defect, such as a chromosomal disorder or recognizable syndrome.

Unclear: if time of exposure during pregnancy was not specified.

I did not consider probable as a classification category because I am not aware of any studies in animals or humans suggesting that exposure to Omeprazole during the period of organogenesis may be associated with birth defects.

Of the eighteen reports of birth defects, I classified sixteen as possible, two as unlikely, and one as unclear. See attached table. Among the sixteen reports of birth defects classified as possible, there were four reports indicating the presence of risk factors for birth defects, including maternal diabetes, febrile illness, and family history of birth defects. Since the etiology of birth defects is thought to be multifactorial, these risk factors could also be considered as alternative explanations for the observed defects. It is also possible that the presence of such risk factors might have enhanced the susceptibility to teratogenesis by Omeprazole.

To be consistent, I am inclined to classify the reports of fetal death and of hypoglycemia, respiratory distress and pneumonia as possible. However, without more information about the pregnancies, it is difficult to be sure that there were no better explanations for these events. In the case of hypoglycemia with respiratory distress and pneumonia, based on the information available, it is difficult to know the actual sequence of events and, therefore, to identify the most likely cause. If one could be sure that pneumonia had occurred first, one might just as easily postulate that infection was the underlying cause of respiratory distress and stress-induced hypoglycemia, without needing to invoke any etiologic role for Omeprazole.

Adolfo Correa, MD, PhD  
09.06.00

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ON ORIGINAL

|    |                      |                            |                       |                        |         |    |                           |
|----|----------------------|----------------------------|-----------------------|------------------------|---------|----|---------------------------|
| 2  | WAES93030842         | myelomeningocele, cleft    | 12 mo, 20 mg          | insulin                | ?       | 28 | possible                  |
| 3  | WAES93030842         | meningo myelocoele, c+p    | entire prg. 40 mg     | antibiotic for cough   | neg     | 28 | Possible                  |
| 4  | 19971000103          | oculo-auricular-fronto-nas | at pregnancy dx       | ranitidine, 2nd        | ?       | 39 | gastric ulcer<br>Unlikely |
| 5  | 19981000099          | VSD                        | 1st month             | promethazine, ran+     |         | 34 | febrile viral<br>Possible |
| 6  | 19951200114          | anencephaly                | 1st trimester         |                        | ntd     | 31 | Possible                  |
| 7  | 9940700090           | anencephaly (prenatal)     | 8-13 weeks gestat     |                        |         | 20 | Unlikely                  |
| 8  | 19950900177          | cleft palate               | time of use unspc.    | gaviscon, ponstan      |         | 30 | Unclear                   |
| 9  | 19951100030          | pyloric stenosis           | 3rd trimester         | ranitidine, 3rd, 18 d  |         | 33 | Possible                  |
| 10 | 90049398             | facial deformity           | 1, 2, 3 trimesters    | ranitidine             |         | 39 | Possible                  |
| 11 | 19990700200          | maxillary fibrous dysplas  | 1st trimester         |                        | ?       |    | Possible                  |
| 12 | 19940900104          | fetal death                | 1st trimester         | amoxicillin, clary     | ?       |    | No defect                 |
| 13 | 19950900045          | chromosomal rearrangem     | 1st trimester, durtn? | zantac                 | ?       |    | Unlikely                  |
| 14 | 19990100187          | anophthalmia, hydrops f    | 1, 2, 3 trimesters    | ?                      |         | 34 | duod ulcer<br>Possible    |
| 15 | 19960800134          | hypoch/resp dist/pneu      | 3rd trimester         | antibiotic, med, clary | ?       | 34 | hrv/guin/psu<br>No defect |
| 16 | 19950200048          | hypoplastic left heart     | 1st trimester         | h2 antag, kfx, caraf   | ?       | 21 | gu an/hx uti<br>Possible  |
| 17 | WAES93061143         | anencephaly                | 1st trimester         | prenatal vitamins      | ?       | ?  | hiatal hernia<br>Possible |
| 18 | 19981000189/D0000714 | limb deform, 1 lower arm   | 1st trimester         | ranitidine             | ?       | 27 | gastritis<br>Possible     |
| 19 | 19951000273          | severe talipes             | 1, 2, 3 trimesters    | folic acid, vitamins   | ntd     | 37 | ge reflux<br>Possible     |
| 20 | 19951000270          | anencephaly                | 1, 2, 3 trimesters    | GIFT (ART)             | talipes | 36 | ge reflux<br>Possible     |

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Received: from cdsyss1.cder.fda.gov  
("port 4110"@cdsyss1.cder.fda.gov [150.148.150.21])  
by mail.cder.fda.gov (PMDF V6.0-24 #42130)  
with SMTP id <01JTUUSSZBW690MVHH@mail.cder.fda.gov>; Wed,  
06 Sep 2000 14:57:35 -0400 (EDT)  
Received: from 198.246.96.75 by cdsyss1.cder.fda.gov with SMTP  
(WorldSecure Server SMTP Relay(WSS) v4.3); Wed, 06 Sep 2000 14:55:32 -0400  
Received: from mcdc-us-smtp4.cdc.gov ([198.246.96.75])  
by ocswall4 via smtpd (for cdsyss1.cder.fda.gov [150.148.150.21])  
with SMTP; Wed, 06 Sep 2000 18:52:49 +0000 (UT)  
Received: from 198.246.96.17 by mcdc-us-smtp4.cdc.gov  
(InterScan E-Mail VirusWall NT); Wed,  
06 Sep 2000 14:56:36 -0400 (Eastern Daylight Time)  
Received: by mcdc-us-imagate.cdc.gov with Internet Mail Service (5.5.2651.58)  
id <SMSBCMW6>; Wed, 06 Sep 2000 14:56:41 -0400  
X-Mailer: Internet Mail Service (5.5.2651.58)  
X-Server-Uid: 00796fd4-893e-11d3-8ed3-0008c75df4f2  
X-WSS-ID: 15A84CA9750255-01-01

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Walsh

**DDMAC ADDENDUM REVIEW**

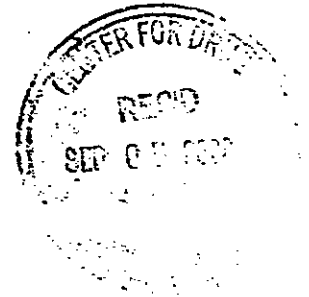
AUG 31 2000

**NDA #** 21-229  
**Drug:** Omeprazole Magnesium Tablets  
**Sponsor:** The Procter & Gamble Co.  
**Identification:** Study 3358 Label Comprehension  
**Date of Document:** January, 1998  
**Reviewer:** Karen Lechter, J.D., Ph.D., HFD-42  
**Review Completed:** August 31, 2000

Attached are two labels for this product. The first is the label studied in the Label Comprehension study. The second is the label proposed with the NDA.

[ ]

Karen Lechter, J.D., Ph.D.



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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

AUG 31 2000

Dear Dr. Kozarek:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We also refer to the August 23, 2000 teleconference between Ms. Linda C. Jones of your firm and Ms. Maria R. Walsh of this Division in which additional information requests were conveyed. Per that teleconference, we have the following requests:

Regarding the post-marketing data for omeprazole magnesium contained in the Safety Update, dated May 25, 2000:

1. Please verify that the total number of patients is 219.
2. Please specify the total number of adverse events both serious and non-serious.
3. For non-serious events, please provide information about the nature of the event, its outcome, and its relatedness to drug. This information may be in narrative or in summary table form.

We also have the following additional request:

Please provide overall commentary on the safety profile of omeprazole magnesium MUPS tablets for OTC switch based on these post-marketing reports.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

YS/ - 8/31/00

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

NDA 21-229

Page 2

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-180/H.Gallo-Torres

HFD-560/L.Chin

D.Shetty

D.Keravich

Drafted by: M. Walsh 8/24/00

Initialed by: L.Chin 8/24/00

S.Aurecchia 8/25/00

L.Talarico 8/25/00

K.Johnson 8/30/00

final: M.Walsh 8/31/00

filename: 21229.August-2000.IR3.doc

INFORMATION REQUEST (IR)

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AUG 21 2000

## MEMORANDUM OF TELECON

DATE: July 6, 2000

APPLICATION NUMBER: NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

## BETWEEN:

The Proctor and Gamble Co.

George Jerdack, Ph.D., Statistician, Section Head

Sangyi Luo, Ph.D., Statistician

Mohammad Hoseyni, Ph.D., Statistician, Associate Director

Tim Balm, Research Fellow

Linda C. Jones, Regulatory Affairs

William Kozarek, Ph.D., Section Head, Regulatory Affairs

AstraZeneca LP

Jose Gallo, Ph.D., Biostatistics

George A. Kummeth, Regulatory Project Manager

Gary P. Horowitz, Ph.D., Executive Director, Regulatory Affairs

## AND

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Steven Aurecchia, M.D., Deputy Director

Lawrence Goldkind, M.D., Medical Officer

Maria R. Walsh, M.S., Regulatory Project Manager

Division of Biometrics II (HFD-715)

Thomas Permutt, Ph.D., Team Leader, Biostatistics

Wen Jen Chen, Ph.D., Biostatistician

SUBJECT: Discussion of June 22, 2000 Information Letter - Statistical Issues

BACKGROUND: AstraZeneca (sponsor) together with The Proctor and Gamble Co., (agent) submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, for the following indications: 1) the relief of heartburn, acid indigestion, and sour stomach; and 2) the prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise.

The FDA issued a June 22, 2000 letter requesting additional information regarding the statistical analyses for Studies 092 and 095. In a submission dated June 29, 2000 (attached), the sponsor requested clarification on three points in our June 22, 2000 letter (listed below).

**TODAY'S CALL:**

**Request No. 1:** Please provide the intent-to-treat (ITT and per protocol (PP) analyses for time-to-onset of sustained adequate relief and time-to-onset of adequate relief for the first, last, and all treated episodes of heartburn.

The FDA clarified that a separate analysis for the first and last episodes should be provided.

**Request No. 2:** Please provide analyses that will add understanding to the efficacy of Prilosec 1 in the OTC setting of heartburn treatment in subjects who take it for episodic heartburn (i.e. less frequent than every 2-3 days).

The FDA said an episode-based analysis, as described in the sponsor's June 29, 2000 submission, is acceptable [i.e. for each subject, include the first episode, and each subsequent episode that is separated >3 days from its most recent (immediately preceding) episode. All subjects would be included in this case and the analysis would be done using episodes without the carry-over effect].

**Request No. 3:** Please provide the following treatment efficacy analyses that eliminate the carry-over effect based on the subjects taking medication more frequently than every 5 days (duration of gastric acid inhibition associated with the use of Prilosec) for the ITT and PP patient populations.

The FDA said the alternative approach, as proposed in the sponsor's June 29, 2000 submission, is acceptable [i.e. similar to the episode-based analyses suggested in number 1 above, where the first episode, plus each subsequent episode that is separated by >4 days from its most recent (immediately preceding) episode would be included].

The FDA requested the following additional analyses.

1. For studies 092 and 095: A stratified analysis, based on the baseline severity of heartburn (i.e. patients having heartburn frequency  $\geq 50\%$  of days and an Average Heartburn Severity score  $\geq 2.5$  versus those who are not in this level) for all endpoints. The rationale for this requested analyses is to determine whether efficacy is limited to severe heartburn sufferers.
2. For studies 005 and 006: A combined (pooled) analyses for all secondary endpoints.

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NDA 21-229

Page 3

A discussion ensued between Dr. Luo and Dr. Chen about the details of the first requested analysis. Dr. Chen requested that the additional data variables be added to those provided in the file named "HB14." He also requested that for both requested analyses, the SAS programs and transport files with data variables be submitted to the NDA.

The FDA said a follow-up letter will be sent to the sponsor detailing the additional analyses requested today. The call was then concluded.

Minutes Preparer: [ BSI ] 8/21/00

Chair Concurrence: [ BSI ] 8/21/00

cc: Original NDA 21-229  
HFD-180/Div. File  
HFD-180/PM/M. Walsh  
HFD-180/S. Aurecchia  
L. Talarico  
HFD-715/T. Permutt  
W. Chen

Drafted: M. Walsh 8/17/00  
Initialed by: W. Chen 8/17/00  
S. Aurecchia 8/18/00  
Final M. Walsh 8/21/00  
filename: 21229.July-2000.telecon.doc

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TELECON

DDMAC REVIEW

AUG 16 2000

**NDA #** 21-229  
**Drug:** Omeprazole Magnesium Tablets  
**Sponsor:** The Procter & Gamble Co.  
**Identification:** Study 3358 Label Comprehension  
**Date of Document:** January, 1998  
**Reviewer:** Karen Lechter, J.D., Ph.D., HFD-42  
**Review Completed:** August 16, 2000

Attached is a detailed review of the label comprehension study for omeprazole magnesium tablets. The attached review was written by DDMAC staff in 1998 in response to the study report submitted under INL . . . . The IND label comprehension report is identical to the one submitted under this NDA.

The tested label was changed in content and organization after the label comprehension study. The labels used in the actual use studies differed substantially from the one studied for comprehension. The label proposed as the final draft for the NDA is similar, but not identical, to the actual use study labels. Therefore, at this point, there is no label comprehension study that evaluates comprehension of the most recent draft of the label.

The attached detailed review from 1998 makes the following general points:

- The most significant concern raised by this study was the potential for use by persons with conditions that require physician consultation according to the label. A substantial proportion (74%) of persons who should contact a physician before use said they would use the product, and did not mention contacting a physician.

As a result of these findings about use by persons who should contact a physician, the sponsor conducted an addendum study. The addendum study was designed to determine whether the wording of the question about using the product accounted for the high incorrect rate among persons who should have consulted a physician before use. The results of the addendum study suggest that the wording of the question did, to some extent, cause some of the incorrect responses. However, when the question was worded in a better way, incorrect response rates were still high among this group (43% incorrect using original question; 31% incorrect using revised wording).

Further questioning resulted in lower rates for incorrect responses. However, these additional questions were leading. The agency believes the responses to the leading questions do not reflect normal consumer understanding of the label. Therefore, the agency does not rely on responses to these questions as indicators of comprehension. Furthermore, the sample size for this study was small—only 29 participants saw the newly worded initial question and 29 saw the question as it was worded in the main study. As a result of the findings in both studies, the agency is concerned that

substantial numbers of consumers who should consult a physician before use may not do so.

- For some of the questions in the main survey, the low-literate (below 9<sup>th</sup> grade reading level) participants scored lower at the 95% confidence interval than the non-low-literate participants. In some cases, only the “sufferers” or “non-sufferers” showed a difference between the low-literate and non-low-literate groups. This was due, in some cases, to the fact that only sufferers were asked some of the questions. Sufferers were consumers who experience heartburn, acid indigestion, or sour stomach. Low-literate participants scored lower in correct responses for four questions, listed in Table 1.

The first item in the table indicates few participants overall stated that the product is for both prevention and treatment. There was a lower percent of correct responses among the low literate non-sufferer participants, compared with non-low-literate non-sufferers. However, most (99%) overall mentioned that the product was for prevention or treatment.

The results producing some concern deal with dosing twice within a 24-hour period. Low literate participants scored 74% correct on this item. It should be noted that the tested label tells consumers not to take more than one tablet in 24 hours. The most recently proposed label says not to take more than one a day, leaving open the possibility of two doses within a 24-hour period, but on different days. However, the most recent label version avoids the need for consumers to understand the 24 hour concept and the need to count the hours since the last dose, and therefore may be easier to understand.

Table 1. Differences in correct responses between non-low-literate and low-literate participants.

| Question Area                                              | Non-Low-Literate Correct Responses (%) | Low Literate Correct Responses (%) |
|------------------------------------------------------------|----------------------------------------|------------------------------------|
| Use for symptoms and prevention (among non-sufferers only) | 17                                     | 7                                  |
| Use during pregnancy (sufferers)                           | 98                                     | 92                                 |
| Amount to take for prevention for 1 meal (sufferers)       | 97                                     | 89                                 |
| Use within 24 hours of earlier dose (sufferers)            | 84                                     | 74                                 |

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The low-literate sufferers were incorrect (19%) more often than the literate sufferers (12%) on the question about the time to take the medication for prevention of symptoms before one meal.

Conclusion

There is evidence that substantial proportions of persons who should consult a physician before use may ignore that recommendation on the label. There are a few parts of this label that might benefit by rewording. The tested label is sufficiently different from the most recently proposed label that the results are inapplicable to the newer label.

[ 15 ]

~~Karen~~ Lechter, J.D., Ph.D.  
Division of Marketing, Advertising,  
and Communications

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ON ORIGINAL

**MEMORANDUM OF TELECON**

**DATE:** August 14, 2000

**APPLICATION NUMBER:** NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

**BETWEEN:**

Name: Bill Kozarek, Ph.D.  
Phone: (513) 622-3131  
Representing: Proctor and Gamble

**AND**

Name: Maria R. Walsh, M.S., Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**SUBJECT:** Proposed indication for the prevention and treatment of heartburn.  
Single-dose studies in IND 54,307

**BACKGROUND:** AstraZeneca (sponsor) together with Proctor and Gamble (agent) submitted NDA 21-229 on January 27, 2000 for Prilosec 1 (omeprazole magnesium) Tablets for: 1) the relief of heartburn, acid indigestion, and sour stomach; and 2) the prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages.

An information request letter, dated June 22, 2000, was sent to Proctor and Gamble and included the following request:

\_\_\_\_\_

\_\_\_\_\_

A response to our letter was submitted on July 20, 2000.

**TODAY'S CALL:** Dr. Kozarek relayed that the statement in the proposed labeling \_\_\_\_\_ was meant as a communication to consumers but if it is a problem for the Agency, the sponsor will delete it and propose new language rather than have it become an issue for the Joint Advisory Committee meeting.

I told Dr. Kozarek that the July 20, 2000 amendment was still under review but that I would communicate his comments to the review team.

Dr. Kozarek also mentioned that three single-dose studies were submitted to IND 54,307 but

NDA 21-229

Page 2

were not included in NDA 21-229 because efficacy was not demonstrated. The safety data was from these studies was included, however.

I told Dr. Kozarek that I would relay this information to the review team. The call was then concluded.

[ 151 ] 8/16/00

Maria R. Walsh, M.S.

Regulatory Project Manager

cc: Original NDA 21-229  
HFD-180/Div. File  
HFD-180/M. Walsh  
HFD-180/H. Gallo-Tores  
L. Goldkind  
M. Avigan  
S. Kress  
S. Aurecchia  
L. Talarico  
HFD-715/W. Chen  
HFD-560/D. Keravich

filename: 21229.August-2000.telecon.doc

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Walsh

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

AUG 10 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Regarding Studies 092 and 095:

1. Please specify, at entry prior to treatment, the proportion of patients that:
  - A. had heartburn symptoms on at least four days per week for three or more months.
  - B. had heartburn symptoms for two to four days per week for three or more months.
  - C. had heartburn symptoms one day per week for three or more months.
  - D. had heartburn symptoms for less than three months.
  - E. had previously been seen by a physician for heartburn.
  - F. had previous endoscopies to rule out GERD-related abnormalities. Please provide the endoscopy findings.
2. Please provide any information regarding recurrence of heartburn within and after three months during the follow-up period after cessation of treatment. Please specify what proportion of patients have restarted heartburn medication, have been seen by a physician, or have undergone endoscopy.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

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ON ORIGINAL

Sincerely,

*ls/ 8-10-00*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-180/M. Avigan

L. Goldkind

H. Gallo-Torres

HFD-560/D. Keravich

Drafted by: M. Walsh 8/7/00

Initialed by: M. Avigan 8/8/00

H. Gallo-Torres 8/10/00

S. Aurecchia 8/10/00

L. Talarico 8/10/00

final: M. Walsh 8/10/00

filename: 21229.August-2000.IR2.doc

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ON ORIGINAL

INFORMATION REQUEST (IR)

Walsh

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

AUG - 9 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Regarding Study 022:

A. Please reanalyze the data by Exclusive Use Per-Subject Basis for the following tables:

- Table 8.1.8 Heartburn History
- Table 8.1.11 Concomitant Drug Therapies
- Table 8.2.8 Number of Dosing Occasions
- Table 8.2.13 Maximum Number of Sequential Dosing Days

B. Please tabulate the responses to all questions on pages 13, 14, and 15 of the Case Report Form related to contact with a doctor/health care practitioner about heartburn and use of Prilosec, specifically, questions 3, 4, 5, 8, and 9.

2. Regarding Study 003:

A. Please provide a summary table of Appendix 2.7.1

B. Please clarify how Table 8.2.19 was derived; specifically, how was the mean percent of effectiveness calculated?

C. Please provide a table for percent effectiveness by each subject for all dosing occasions, dosing occasions on first dose, and dosing occasions with backup medication use.

D. Please provide demographics (in WORD document) for the lost-to-follow-up patients.

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3. Regarding Studies 003, 067, 014, 022, and 091:

- A. Please provide a table for the pregnancy test results for each pregnancy test.
- B. Please provide, in separate datasets for each study, a full accounting of all subjects who enrolled [i.e. by participation status, inclusion/exclusion criteria, investigator, further exclusion, subject withdrawal, received study medication, completion status (return of Product Use Journal?), etc.].
- C. Please provide, in separate datasets for each study, except Study 091, the information from the Product Use Journal (dosing information) for all subjects with incomplete data (the subjects excluded from the ITT dataset).
- D. Please provide confidence intervals for all primary endpoints for ITT subjects:

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

*LS* *P-9-23*

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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ON ORIGINAL

*[Handwritten signature]*

NDA 21-229

Page 3

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/M. Walsh

HFD-180/H. Gallo-Torres

HFD-560/D. Keravich

D. Shetty

L. Chin

Drafted by: M. Walsh 8/8/00

Initialed by: D. Shetty 8/8/00

L. Chin 8/8/00

L. Lu 8/8/00

S. Aurecchia 8/8/00, 8/9/00

L. Talarico 8/8/00, 8/9/00

revised: M. Walsh 8/9/00

final: M. Walsh 8/9/00

filename: 21229.August-2000.IR.doc

APPEARS THIS WAY  
ON ORIGINAL

INFORMATION REQUEST (IR)

Walsh

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

AUG - 8 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Regarding Actual Use studies 003, 014, 022, and 067:

1. Please submit the actual labels used in these studies.
2. Please specify if subjects were required to pay for their medication.
3. Please specify, for each subject (verbatim, including contraindicated medications), the

reasons for the following :

A. Study 003 (p. 40, Table B):

213 subjects decided not to participate.

B. Study 014 (p. 33, Table B):

66 subjects were not qualified for enrollment.

10 subjects were withdrawn by the investigator.

C. Study 022 (p. 42, Table B):

113 subjects decided the medicine was not appropriate for use.

19 subjects did not meet inclusion/exclusion criteria.

8 subjects were withdrawn by the investigator.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

BL 8-6-00

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-229  
HFD-180/Div. Files  
HFD-180/PM/M. Walsh  
HFD-180/H. Gallo-Torres  
HFD-560/D. Keravich  
D. Shetty

Drafted by: M. Walsh 7/26/00  
Initialed by: D. Shetty 7/28/00  
S. Aurecchia 8/3/00  
L. Talarico 8/4/00  
final: M. Walsh 8/7/00  
filename: 21229.July-2000.IR3.doc

APPEARS THIS WAY  
ON ORIGINAL

INFORMATION REQUEST (IR)

Walsh

MEMORANDUM OF TELECON

DATE: August 8, 2000

APPLICATION NUMBER: NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

BETWEEN:

The Proctor and Gamble Co.  
George Jerdack, Ph.D., Statistician, Section Head  
Sangyi Luo, Ph.D., Statistician  
Tim Balm, Research Fellow  
Jan Hess, Data Management  
Beverly Worsham, Data Management  
Linda C. Jones, Regulatory Affairs  
William Kozarek, Ph.D., Section Head, Regulatory Affairs  
Kevin Ross, Regulatory Affairs

AND

Division of Biometrics II (HFD-715)  
Wen Jen Chen, Ph.D., Biostatistician

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)  
Maria R. Walsh, M.S., Regulatory Project Manager

SUBJECT: Information request re: Efficacy Studies 092, 095, 005, 006, 171, and 183

BACKGROUND: AstraZeneca (sponsor) together with The Proctor and Gamble Co. (agent) submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, for the following indications: 1) the relief of heartburn, acid indigestion, and sour stomach; and 2) the prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages.

---

At the request of the statistical reviewer, Dr. Wen Jen Chen, I scheduled this teleconference to discuss questions regarding missing data from efficacy studies 092, 095, 005, 006, 171, and 183.

TODAY'S CALL: The following questions were presented to the sponsor:

- 1: How are the missing data handled across the studies?
- 2: What is the percent of missing data for each study by treatment group for the primary efficacy endpoint?

- 3: In the submitted data sets, was missing data replaced with other data and, if so, how was it replaced?

The sponsor said the handling of missing data is described in Appendix 1.9.1 for each study. For studies 092, 095, 005, and 006: If subjects took back-up medication, they were considered treatment failures. If no back-up medication was taken, missing efficacy evaluations were imputed using the last observation carried forward. For studies 171 and 183: Missing data were not imputed except for the analysis of the primary efficacy endpoint, i.e. if the response to the 24-hour heartburn question on Day 1 is missing, then the subject will be considered a treatment failure.

The sponsor said the number of subjects who had missing data is listed in Table 1.9.2.36 for Study 092; Table 1.9.2.39 for Study 095; Table 8.1.5 for studies 005 and 006; and Table 8.1.10 for studies 171 and 183.

Ms. Jones said a follow-up correspondence will be faxed to the Agency containing a listing of all documents referenced during this teleconference. The call was then concluded.

Post-teleconference note: The follow-up correspondence from the sponsor, dated August 11, 2000 is attached.

[ M/W ] 8/17/00

Maria R. Walsh, M.S.  
Regulatory Project Manager

cc: Original NDA 21-229  
HFD-180/Div. File  
HFD-180/PM/M. Walsh  
HFD-180/S. Aurecchia  
L. Talarico  
HFD-715/W. Chen  
T. Permutt

APPEARS THIS WAY  
ON ORIGINAL

Drafted: M. Walsh 8/16/00  
Initialed by: W. Chen 8/16/00  
Final: M. Walsh 8/17/00  
filename: 21229.August-2000.telecon2.doc

TELECON

Walsh

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

JUL 31 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Clinical section of your submission and have the following information request. We need your prompt written response to continue our evaluation of your NDA.

Please submit all available information (clinical studies and literature) by dose of omeprazole (i.e. 10, 20, \_\_\_\_\_ mg/day) for the following:

1. Changes in serum gastrin levels for short- and long-term use.
2. Safety profile, including the rates and severity of rare serious adverse events; common adverse events; and drug interactions.
3. Effect on basal acid output (BAO) after single and consecutive multiple doses.

Information on individual distribution data as well as population statistics should be included.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

[Signature] 7/31/00

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-229

Page 2

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/M.Walsh

HFD-180/L.Goldkind

M.Avigan

S.Kress

H.Gallo-Torres

HFD-560/D.Keravich

Drafted by: M. Walsh 7/19/00

Initialed by: L. Goldkind 7/19/00

M. Avigan 7/24/00

H. Gallo-Torres 7/26/00

S. Aurecchia 7/26/00

K. Johnson 7/28/00

Revised: M. Walsh: 7/20/00

final: M. Walsh 7/31/00

filename: 21229.July-2000.IRletter2.doc

INFORMATION REQUEST (IR)

APPEARS THIS WAY  
ON ORIGINAL

Walsby

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

JUL 17 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We also refer to your submission dated June 29, 2000, which includes your request for clarification on three information requests regarding Studies 1997092 and 1997095, contained in our June 22, 2000 letter.

We further refer to the July 6, 2000 teleconference between representatives of your firm and AstraZeneca LP and members of this Division in which your June 29, 2000 submission was discussed. As per that discussion, we have the following comments and requests:

1. Regarding our Request No. 1 - "Please provide the intent-to-treat (ITT) and per protocol (PP) analyses for time-to-onset of sustained adequate relief and time-to-onset of adequate relief for the first, last, and all treated episodes of heartburn:"

Your proposal to provide a separate analysis for each episode is acceptable. However, you should provide an analysis for the first and last episodes only.

2. Regarding our Request No. 2 - "Please provide analyses that will add understanding to the efficacy of Prilosec 1 in the OTC setting of heartburn treatment in subjects who take it for episodic heartburn (i.e. less frequent than every 2-3 days):"

Your proposal for an episode-based analysis, as stated in your June 29, 2000 submission, is acceptable.

3. Regarding our Request No. 3 - "Please provide the following treatment efficacy analyses that eliminate the carry-over effect based on the subjects taking medication more frequently than every 5 days (duration of gastric acid inhibition associated with the use of Prilosec) for the ITT and PP patient populations:"

Your proposal for an episode-based analysis, as stated in your June 29, 2000 submission, is acceptable.

4. Please define the stratification variable HBPS with the following two levels: level 1 – patients having Heartburn frequency  $\geq 50\%$  of days and Average Heartburn Severity score  $\geq 2.5$  during the placebo run-in phase; level 2 – patients not in level 1. Then, perform the following statistical analyses to compare the effects between two treatment groups for both ITT and PP patient populations:
  - A. Cochran-Mantel-Haenszel (CMH) test on endpoints SCR, CR, SAR, AR, BU, and OE, with HBPS as a stratification variable for the first- and last- treated episodes.
  - B. Log-rank test on Time to Sustained Complete Relief, Time to complete Relief (within 3 hours), time to Sustained Adequate Relief, Time to Adequate Relief, and Time to Backup Medication (Gelusil) use, with HBPS as a stratification variable for the first- and last- treated episodes.
  - C. GEE method on SCR, CR, SAR, AR, BU, and OE using treatment, investigator, episode, HBPS (if no interaction between treatment and HBPS was detected, otherwise perform GEE separately for each level of HBPS), as model parameters using all treated episodes. In this analysis, treat episode as a covariate.
  - D. GEE method on SCR, CR, SAR, AR, BU, and OE using treatment, investigator, episode, HBPS (if no interaction between treatment and HBPS was detected, otherwise, perform GEE separately for each level of HBPS), as model parameters using the first episode and each subsequent episode that is separated by  $> 4$  days from its most recent (immediately preceding) episode, described in your June 29, 2000 submission. In this analysis, treat episode as a covariate.

The variables used in the above analyses (#1-#4) should be properly added to those provided in the electronic file named "HB14." Then, the modified HB14 file and the related SAS programs should be submitted to the Agency.

5. For Studies 1998005 and 1998006, please provide a combined (pooled) analysis for all secondary endpoints.

The SAS programs and transport files with variables used in the above analysis should be submitted to the Agency.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

KS/ 7/17/00

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/PM/M. Walsh

HFD-180/L. Goldkind

H. Gallo-Torres

S. Aurecchia

HFD-715/W. Chen

T. Permutt

HFD-560/D. Keravich

APPEARS THIS WAY  
ON ORIGINAL

Drafted by: M. Walsh 7/10/00

Initialed by: W. Chen 7/10/00

L. Goldkind 7/11/00

S. Aurecchia 7/11/00

K. Johnson 7/14/00

final: M. Walsh 7/17/00

filename: 21220.July-2000.IR.doc

INFORMATION REQUEST (IR)

Walsh

NDA 21-229

JUL 10 2000

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We also refer to your correspondence dated April 14, 2000, requesting a waiver for pediatric studies under 21 CFR 314.55(c) in children under the age of 12 with episodic heartburn.

We have reviewed the information in your April 14, 2000 correspondence. We are deferring our decision to grant or deny a waiver until review of your NDA is completed.

If you have questions, please contact Maria R. Walsh, Regulatory Project Manager, at (301) 443-8017.

Sincerely,

LS/ 7-10-00

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-229  
Page 2

cc:

Original NDA 21-229  
HFD-180/Division file  
HFD-180/RPM/M. Walsh  
HFD-180/S.Aurecchia  
L. Talarico  
HFD-103/V.Raczkowski

Drafted by: M. Walsh 6/26/00  
Initialed by: S.Aurecchia 7/3/00  
L. Talarico 7/3/00  
Final: M. Walsh 7/10/00  
filename: 21229.June-2000.adviceletter.peds.doc

**GENERAL CORRESPONDENCE (GC)**

APPEARS TO BE  
ON ORIGINAL

Walsh

NDA 21-229

INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

JUN 22 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Clinical and Statistical sections of your submission and have the following information requests regarding Studies 1997092 and 1997095. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide the intent-to-treat (ITT) and per protocol (PP) analyses for time-to-onset of sustained adequate relief and time-to-onset of adequate relief for the first, last, and all treated episodes of heartburn.
2. Please provide analyses that will add understanding to the efficacy of Prilosec 1 in the OTC setting of heartburn treatment in subjects who take it for episodic heartburn (i.e. less frequent than every 2-3 days).
3. Please provide the following treatment efficacy analyses that eliminate the carry-over effect based on the subjects taking medication more frequently than every 5 days (duration of gastric acid inhibition associated with the use of Prilosec) for the ITT and PP patient populations:
  - A. GEE method on sustained complete relief (SCR), complete relief within the first hour (CR), sustained adequate relief (SAR), adequate relief within the first hour (AR), backup medication use (BU), and drug overall assessment (OE) using treatment, investigator, episode, and treatment\*episode as model parameters. In this model, treat episode as a covariate.
  - B. GEE method on SCR, CR, SAR, AR, BU, and OE using treatment, investigator, episode, and treatment\*investigator as model parameters for treated episodes separated by > 4 days from most recent episode. In this model, treat episode as a covariate.
  - C. GEE method on SCR, CR, SAR, AR, BU, and OE using treatment, investigator, and episode as model parameters for treated episodes separated by > 4 days from most recent

episode. In this model, treat episode as a covariate.

- D. For treated episodes separated by > 4 days from most recent episode. perform a Cochran-Mantel-Haenszel test to compare the treatment efficacy for each Ome-Mg dose versus placebo and Ome-mg 20 versus Ome-Mg 10, using investigator as a stratification factor and the Breslow-Day test for odds homogeneity across investigators between two treatment groups.
  - E. For treated episodes separated by > 4 days from most recent episode. perform a Cochran-Mantel-Haenszel test to compare the treatment efficacy for each Ome-Mg dose versus placebo and Ome-Mg 20 versus Ome-Mg 10 without using stratification factors.
4. Please provide the SAS programs and SAS data sets (.sd2) used to perform the above statistical efficacy analyses, separately for each item (item 1 to item 3). for both ITT and PP patient populations.
  5. Please provide an analysis that supports the claim that heartburn \_\_\_\_\_ is treated and prevented. This analysis should go beyond the provided information of subjects who were enrolled because they had recently experienced heartburn because this information appears to document meal-induced heartburn but not stress-induced heartburn.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

[KJ] 6/22/00

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
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NDA 21-229

Page 3

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/M. Walsh

HFD-180/H.Gallo-Torres

L.Goldkind

HFD-715/W.Chen

HFD-560/D.Keravich

DISTRICT OFFICE

Drafted by: M. Walsh 6/20/00

Initialed by: W.Chen 6/20/00

T. Permutt 6/21/00

L.Goldkind 6/21/00

H.Gallo-Torres 6/22/00

S.Aurecchia 6/22/00

K.Johnson 6/22/00

final: M. Walsh 6/22/00

filename: 21229.June-2000.IRletter.doc

INFORMATION REQUEST (IR)

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-229

Ward  
INFORMATION REQUEST LETTER

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

APR 14 2000

Dear Dr. Kozarek:

Please refer to your January 27, 2000 new drug application for Prilosec 1 (omeprazole magnesium) Tablets.

We are reviewing the Biopharmaceutics and Clinical sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Biopharmaceutics

The analytical assay methods validation for the individual pharmacokinetic studies cannot be located in the application. If submitted, please specify the location of this information (i.e. electronic folder/pages). If this information is not included in the application, please submit a summary for each of the studies.

2. Clinical

A. Regarding the Labeling Comprehension Study 3358:

- 1) Please submit the screening questionnaire and the main questionnaire and script.
- 2) Please submit any advertising/recruiting materials used to attract participants.
- 3) Please submit a breakdown of responses to questions in terms of actual answers given and specify the percentages for each response. For example, if 90% of participants gave acceptable responses to a question, specify what percent gave response X, response Y, and response Z. Specify which responses were scored correct, acceptable, and incorrect.

B. Regarding Foreign Marketing History and Post-Marketing Experience:

Omeprazole

- 1) Please submit a summary of the foreign marketing history of omeprazole, listing each country where it is approved and marketed, including time of launch, and whether it is marketed as a prescription or over-the-counter (OTC) drug. If OTC, specify whether it is "behind the counter" (pharmacy only) or not.
- 2) Please submit full details of all deaths and serious adverse reactions associated with the use of omeprazole post-marketing.

Omeprazole Magnesium

- 1) For each country marketing omeprazole magnesium, please specify the formulation marketed and whether it is marketed as a prescription or OTC drug. If OTC, specify whether it is "behind the counter" (pharmacy only) or not. Also, include marketing extent.
- 2) Please submit all post-marketing safety data for omeprazole magnesium, including full details of all deaths and serious adverse reactions.

C. Labeling

- 1) Please provide a layout of the formatting specifications for the Drug Facts section of the labeling (refer to 21CFR 201.66 and the example attached).
- 2) Please submit the approved prescription labeling for both omeprazole and omeprazole magnesium from the following countries: Canada, Germany, United Kingdom, and Australia. In addition, please submit the labeling for all countries in which omeprazole and/or omeprazole magnesium are approved OTC. All labeling in a foreign language should be submitted with an English translation.
3. Please provide documentation from the Swedish regulatory authority summarizing the basis for approval of omeprazole magnesium for OTC use in Sweden. This documentation should include a listing of the pivotal studies and a succinct description of their design, endpoints of evaluation, and main results. A synopsis of usage studies should also be provided.

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-229

Page 3

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely.

*JSI 4/12/00*

Kati Johnson  
Supervisory Consumer Safety Officer  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

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NDA 21-229

Page 4

cc:

Archival NDA 21-229

HFD-180/Div. Files

HFD-180/M. Walsh

HFD-180/H. Gallo-Torres

L. Goldkind

M. Avigan

S. Kress

HFD-870/S. Doddapaneni

S. Al-Fayoumi

HFD-40/K. Lechter

HFD-560/D. Keravich

H. Cothran

L. Chin

L. Katz

Drafted by: M. Walsh 3/20/00

Initialed by: H. Gallo-Torres 3/20/00

S. Aurecchia 3/21/00

K. Lechter 3/21/00

L. Chin 4/7/00

L. Katz 4/10/00

K. Johnson 4/12/00

final: M. Walsh 4/12/00

filename: 21229.April-2000.IRletter.doc

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ON ORIGINAL

INFORMATION REQUEST (IR)

ORIGINAL

Procter & Gamble

Dr Goldkind

The Procter & Gamble Company  
Health Care Research Center  
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

NDA 21-229

ORIG AMENDMENT

[ 151 ]

April 14, 2000

Lilia Talarico, M.D., Director  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Dear Dr. Talarico:

**Re: NDA 21-229: Prilosec 1™ (omeprazole magnesium) Tablets  
Waiver Request for Pediatric Testing of Prilosec 1™ (omeprazole magnesium) Tablets**

This is in follow-up to the Agency's letter dated 2/16/00 regarding pediatric testing requirements for Prilosec 1 (omeprazole magnesium) tablets pursuant to 21 CFR 314.55. At this time we are requesting a waiver for pediatric testing in children under the age of 12 with episodic heartburn for Prilosec 1 (omeprazole magnesium) tablets. Please note that our proposed label restricts usage of the product to 12 years of age and greater. Usage of the product by this age group is supported by well-controlled and Actual Use studies included in the NDA.

Our request for a waiver for pediatric testing in children under 12 with episodic heartburn for Prilosec 1 is based on the following:

- 1) In pediatric populations under 12 years of age, heartburn severe enough to require treatment should be evaluated by a physician, and treatment should be directed and overseen by a health professional.

**BEST POSSIBLE COPY**

NDA 21-229

Prilosec 1™ (omeprazole magnesium) Tablets

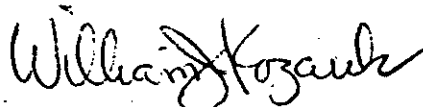
Page 2

- 2) Other treatments such as Antacids (e.g., \_\_\_\_\_) and Histamine H<sub>2</sub> receptor antagonists (e.g., \_\_\_\_\_) are approved for the treatment of heartburn in pediatric patients.
- 3) Prilosec 1 is not likely to be used in a substantial number of pediatric patients with episodic heartburn. IMS National Disease and Therapeutic Index data for the calendar year 1999 indicate that the number of physician mentions of Heartburn [ ] diagnosed within the patient population age 0 to 11 years was [ ] This is less than the FDA defined cut-off of [ ] patients.

Please be advised that pediatric protocols have been submitted to FDA for the R<sub>x</sub> omeprazole capsule formulation under [ ] AstraZeneca LP will generate data for pediatric use of omeprazole under a physician's care. Additionally, studies have shown that the relative bioavailability of omeprazole magnesium tablets is similar to the R<sub>x</sub> omeprazole capsule formulation.

Please do not hesitate to contact either myself at (513) 622-3131 or, in my absence, Linda Jones at (513) 622-3176 should you have any questions.

Sincerely Yours,



William J. Kozarek, Ph.D.  
Section Head, Regulatory Affairs

APPEARS THIS WAY  
ON ORIGINAL

cc: Mr. Kerry Rothschild, Regulatory Project Manager,  
OTC Division (hard copy of cover letter only)

**BEST POSSIBLE COPY**

**PEDIATRIC STUDY DEFERRAL**

Pediatric protocols have been submitted to FDA for omeprazole capsules under the original NDA 19-810. Astra Zeneca LP will generate data for the pediatric use of omeprazole under a physician's care. We are seeking approval for the OTC product for ages 12 and greater. We therefore request deferral of this requirement for the OTC product.

APPEARS THIS WAY  
ON ORIGINAL

Curran

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** March 16, 2000  
**Time:** 3:00 p.m. - 4:00 p.m.  
**Location:** Parklawn Building, Conference Room 18B-37

**Application:** NDA 21-229  
 Prilosec I (omeprazole magnesium) Tablets

**Type of Meeting:** Team Meeting

**Meeting Chair:** Steven Aurecchia, M.D., Deputy Director, HFD-180

**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager

### Attendees:

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Steven Aurecchia, M.D., Deputy Director  
 Hugo Gallo-Torres, M.D., GI Medical Team Leader  
 Lawrence Goldkind, M.D., Medical Officer  
 Mark Avigan, M.D., Medical Officer  
 Sheldon Kress, M.D., Medical Officer  
 Maria R. Walsh, M.S., Regulatory Project Manager

#### Division of Over-The-Counter Drug Products (HFD-560)

Linda Katz, M.D., Deputy Director  
 Ling Chin, M.D., Medical Officer

**Background:** AstraZeneca LP, through their agent, The Proctor & Gamble Co., submitted NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets, on January 27, 2000 for the prevention and treatment of heartburn (OTC indications). This application is being jointly reviewed by the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and the Division of Over-The-Counter Drug Products (HFD-560). A meeting of the medical review team was held to discuss the review of the safety data included in the application.

**Meeting:** After some discussion, it was decided that HFD-180 will review the safety data in the clinical efficacy trials for omeprazole magnesium tablets and the post-marketing experience for omeprazole delayed-release capsules (available as prescription in U.S. and foreign countries). HFD-560 will review the safety data in the actual use studies for omeprazole magnesium tablets and the post-marketing experience for omeprazole magnesium tablets (available as prescription in foreign countries and as OTC in Sweden only). HFD-180 will also review the literature for post-marketing experience for omeprazole (all formulations) but will consult all OTC-related literature to HFD-560 for review. HFD-560 will consider the overall risk/benefit of omeprazole magnesium tablets.

NDA 21-229

Page 2

Minutes Preparer: [ ISI ] 4/19/00

Chair Concurrence: [ ISI ] 4/19/00

cc:

Orig NDA 21-229

HFD-180/Division file

HFD-180/PM/M. Walsh

HFD-560/D. Keravich

Drafted: M. Walsh 4/17/00

Initialed by: H. Gallo-Torres 4/18/00

S. Aurecchia 4/18/00

Final: M. Walsh 4/19/00

filename: 21229.March-2000.team.meeting.minutes.doc

MEETING MINUTES

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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** March 7, 2000  
**Time:** 12:00 p.m. - 1:00 p.m.  
**Location:** Conference Room "K", Parklawn Building/Corporate Blvd. Building (via teleconference).

**Application:** NDA 21-229; Prilosec 1 (omeprazole magnesium) Tablets

**Type of Meeting:** 45-day filing/planning meeting

**Meeting Chair:** Steven Aurecchia, M.D., Deputy Director, HFD-180

**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

### Attendees:

Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)

Lilia Talarico, M.D., Director  
Steven Aurecchia, M.D., Deputy Director  
Hugo Gallo-Torres, M.D., Ph.D., GI Team Leader  
Lawrence Goldkind, M.D., Medical Officer  
Mark Avigan, M.D., Medical Officer  
Scheldon Kress, M.D., Medical Officer  
Liang Zhou, Ph.D., Chemistry Team Leader  
Arthur Shaw, Ph.D., Chemistry Reviewer  
Jasti Choudary, Ph.D., Pharmacology Team Leader  
Timothy Robison, Ph.D., Pharmacology Reviewer  
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Biometrics III (HFD-720)

Paul Flyer, Ph.D., Biostatistics Team Leader

Division of Pharmaceutical Evaluation II (HFD-870)

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader  
Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Over-The-Counter Drugs (DOTCDP) (HFD-560)

Charles Ganley, M.D., Director  
Linda Katz, M.D., M.P.H., Deputy Director  
Ling Chin, M.D., M.P.H., Medical Officer  
Mary S. Robison, Regulatory Review Chemist  
Helen Cothran, Team Leader  
Rosemary Cook, Chief, Project Management Staff  
Kerry Rothschild, Regulatory Project Manager  
Daniel Keravich, Regulatory Project Manager

Division of Drug Marketing, Advertising, and Communications (HFD-40)  
Karen Lechter, J.D., Ph.D., Social Science Analyst

Advisors and Consultants Staff (HFD-21)  
Sandra Titus, Executive Secretary, Non-Prescription Drugs Advisory Committee

**Background:** AstraZeneca LP submitted NDA 21-229. Prilosec 1 (omeprazole magnesium) Tablets, through their agent, Proctor & Gamble, on January 27, 2000 for the following over-the-counter (OTC) indications: 1) treatment of heartburn, acid indigestion, and sour stomach; and 2) prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages

**Meeting:**

**1. Administrative**

Filing issues: None

Administrative issues/requests: This drug product was recently approved for OTC use in Sweden. The Swedish OTC labeling was requested on March 1, 2000 by DGCDP.

**2. Chemistry, Manufacturing, and Controls**

Filing issues: None

Scientific issues/requests: None

**3. Nonclinical Pharmacology**

Filing issues: None

Scientific issues/requests: None

**4. Biopharmaceutics**

Filing issues: None

Scientific issues/requests: The analytical assay methods validation for the individual pharmacokinetic studies cannot be located in the application. If submitted, the sponsor should specify the location of this information (i.e. electronic folder/pages). If this information is not included in the application, the sponsor should submit a summary for each of the studies.

This comment will be included in an information request letter to be drafted by Maria Walsh.

**5. Biostatistics**

Filing issues: None

Scientific issues/requests: None

**6. Clinical/DGCDP (Efficacy studies/Safety):**

Filing issues: None

Scientific issues/requests: None

**7. Clinical/DOTCDP (Actual Use studies/Safety):**

Filing issues: None

Scientific issues/requests:

1. The full foreign marketing history of Prilosec 1 (omeprazole magnesium) Tablets should specify whether approved for prescription or OTC use. If OTC use, it should be specified whether it is "behind the counter" (pharmacy only) or not.
2. The full foreign marketing history of Prilosec (omeprazole) Delayed-Release Capsules, including, list of countries where approved and marketed, whether prescription or OTC, and marketing extent, should be submitted.
3. All information available on adverse events, including case narratives, should be provided.

Dr. Chin will e-mail Maria Walsh with a detailed list of information requests. These requests will be included in an information letter to be drafted by Maria Walsh.

**8. Clinical/DDMAC (Labeling Comprehension study):**

Filing issues: None

Scientific issues/requests:

1. The questionnaire used in the study should be submitted.

2. Any advertising/recruiting materials used to attract participants should be submitted.
3. Results should be broken out by actual answers (i.e. how many people answered and in what way).

Dr. Lechter will e-mail Maria Walsh with a detailed list of information requests. These requests will be included in an information request letter to be drafted by Maria Walsh.

**9. Review Timeline:**

Dr. Aurecchia said that DGCDP is targeting the [ ] . He explained that this application includes six pivotal efficacy studies and a large amount of post-marketing safety information, most of which is special safety considerations, and will be discussed at a Joint Advisory Committee meeting. This issue has been discussed with Dr. Florence Houn, Director, Office of Drug Evaluation III (ODE III), and based upon the current workload of DGCDP and the size of the current application, ODE III is amenable to the [ ] target date. Dr. Katz said that DOTCDP prefers to target the [ ] due date [ ] . After some discussion, it was agreed that the [ ] due date will be targeted.

Final review due dates were discussed. DOTCDP suggested that reviews should be completed by [ ] to allow a two-month buffer for completion of review issues and final sign-off. Dr. Aurecchia said DGCDP is targeting draft review due dates at this time. This issue will be addressed at the first team meeting.

Scheduling of team meetings was discussed. DOTCDP prefers monthly team meetings whereas DGCDP prefers bimonthly team meetings. It was agreed that monthly meetings will be scheduled but could be canceled each month if deemed unnecessary.

**10. Advisory Committee Dates:**

Ms. Titus said the pre-arranged dates for the Non-Prescription Drugs Advisory Committee meetings are: October 19 and 20, 2000 [ ] . Dr. Gallo-Torres expressed his preference for the [ ] dates to allow the maximum amount of time to review the large amount of efficacy data and safety information. Dr. Katz said the [ ] dates would not allow enough time for completion of review issues, labeling negotiations with the sponsor, and Office level sign-off. The possibility of a [ ] meeting was discussed but Ms. Titus said it would have to be scheduled in early [ ] and both Divisions did not consider the difference of two-three weeks particularly advantageous. After some discussion, Dr. Aurecchia agreed that if this application requires Office level review, then the October dates should prevail. Ms. Titus reminded the

Divisions that the FDA background packages are due 18 working days before the meeting and the sponsor's background packages are due 22 working days before the meeting.

**10. Safety Review**

Responsibility for the review of the safety data was briefly discussed. It was agreed that DGCDP will review the safety data from the clinical trials. Dr. Gallo-Torres said that normally, DOTCDP reviews the post-marketing safety data. However, this application includes a large section of special safety information that has been considered by DGCDP in conjunction with various supplements over the last 10 years since U.S. approval of Prilosec (omeprazole) Delayed-Release Capsules. Therefore, responsibility for review of this information requires further deliberation. It was agreed that a separate team meeting of the Medical Officers would be scheduled next week to discuss this issue.

**Conclusions**

1. NDA 21-229, Prilosec 1 (omeprazole magnesium) Tablets will be filed on March 27, 2000.
2. The ~~one~~ month due date (E ~~\_\_\_\_\_~~ ) will be targeted.
3. The Joint Non-Prescription Drugs and Gastrointestinal Drugs Advisory Committee meeting will be held in October 2000.
4. Monthly team meetings will be scheduled.
5. Final review due dates will be addressed at the next team meeting.
6. Responsibility of the review of the post-marketing safety information will be discussed at a special team meeting of the Medical Officers to be scheduled next week.

Minutes Preparer: [ *RS* ] 4/17/00

Chair Concurrence: [ *RS* ]

4/17/00

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Meeting Minutes  
Page 6

cc: Original NDA 21-229  
HFD-180/Div. Files  
HFD-180/Meeting Minutes files  
HFD-180/PM/M. Walsh  
HFD-180/S.Aurecchia  
H.Gallo-Torres  
L.Goldkind  
M.Avigan  
S.Kress  
L.Zhou  
A.Shaw  
J.Choudary  
T.Robison  
HFD-715/P.Flyer  
HFD-870/S.Doddapaneni  
S.Al-Fayoumi  
HFD-560/C.Ganley  
L.Katz  
L.Chin  
M.Robinson  
H.Cothran  
R.Cook  
D.Keravich  
HFD-40/K.Lechter  
HFD-21/S.Titus

APPEARS  
ON DRINK

Drafted by: M. Walsh 3/14/00  
Initialed by: S.Doddapaneni 3/14/00  
H.Gallo-Torres 3/14/00  
L.Talarico 3/14/00  
S.Aurecchia 3/16/00  
L.Chin (comments received by fax 4/14/00)  
L.Katz (comments received by fax 4/14/00)  
final: M. Walsh 4/17/00  
filename: 21229.March-2000.45dayminutes.doc

MEETING MINUTES

MAR - 1 2000

**Division of Gastrointestinal & Coagulation Drug Products**

**ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION**

**Application Number:** NDA 21-229

**Name of Drug:** Prilosec 1 (omeprazole magnesium) 20 mg Tablets

**Sponsor:** AstraZeneca LP/Proctor & Gamble

**Material Reviewed**

**Type of Submission (i.e., paper, electronic, or combination):** Electronic

**Submission Date:** January 27, 2000

**Receipt Date:** January 28, 2000

**Filing Date:** March 27, 2000

**User-fee Goal Date(s):** \_\_\_\_\_

**Proposed Indications:**

1. Treatment of heartburn, acid indigestion, and sour stomach.
2. Prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages

**Other Background Information:** The archival copy of this NDA is in electronic format (CD-ROMs) and is available through the electronic document room. There is one archival paper volume containing all administrative documents which require an original signature (i.e. cover letter, Form FDA 356h, patent information and certification, debarment certification, and financial disclosure) as well as other administrative documentation (field copy certification, user fee cover sheet, exclusivity statement, pediatric study deferral, and comprehensive index).

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## Review

PART I: OVERALL FORMATTING<sup>a,d,e</sup>

| [Note: Items 1,2,3,4, & 5 must be submitted in paper with original signature.] | Y | N | COMMENTS<br>(If paper: list volume & page numbers)<br>(If electronic: list folder & page numbers)                                                                                      |
|--------------------------------------------------------------------------------|---|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. Cover Letter                                                                | X |   | Vol. 1.1, page 2.                                                                                                                                                                      |
| 2. Form FDA 356h                                                               | X |   | Vol. 1.1, pages 8-9.                                                                                                                                                                   |
| a. Establishment information<br>b. Reference to DMF(s) & Other Applications    | X |   | Vol. 1.1, pages 10-14.                                                                                                                                                                 |
|                                                                                | X |   | Vol. 1.1, page 15.                                                                                                                                                                     |
| 3. Patent information & certification                                          | X |   | Vol. 1.1, pages 16-21.                                                                                                                                                                 |
| 4. Debarment certification (Note: Must have a definitive statement)            | X |   | Vol. 1.1, page 25.                                                                                                                                                                     |
| 5. Financial Disclosure                                                        | X |   | Vol. 1.1, pages 38-92.                                                                                                                                                                 |
| 6. Comprehensive Index                                                         | X |   | mainfolder\ndatoc.pdf. pages 84-108.                                                                                                                                                   |
| 7. Pagination                                                                  | X |   | Each volume folder is paginated separately.                                                                                                                                            |
| 8. Summary Volume                                                              | X |   | summary\summary.pdf, pages 1-324.                                                                                                                                                      |
| 9. Review Volumes                                                              | X |   | A paper copy of each technical section is provided as a review aid.<br>Chemistry: Vol. 1.4.<br>Pharm/Tox: Vols. 1.5-1.10.<br>Biopharm: Vols. 1.11-1.25.<br>Clinical: Vols. 1.27-1.153. |
| 10. Labeling (PI, container, & carton labels)                                  | X |   |                                                                                                                                                                                        |
| a. unannotated PI                                                              | X |   | labeling\labeling.pdf. page 12.                                                                                                                                                        |
| b. annotated PI                                                                | X |   | summary\summary.pdf. pages 24-30.                                                                                                                                                      |
| c. immediate container                                                         | X |   | labeling\labeling.pdf. page 14 (blister).                                                                                                                                              |

|                                                                                                             |   |   |                                                                                                             |
|-------------------------------------------------------------------------------------------------------------|---|---|-------------------------------------------------------------------------------------------------------------|
| d. carton                                                                                                   | X |   | labeling\labeling.pdf, page 10. The annotated carton text can be found in summary\summary.pdf, pages 31-39. |
| e. foreign labeling (English translation)                                                                   |   | X | Approved in Sweden for OTC use. Requested Swedish OTC labeling.                                             |
| 11. Foreign Marketing History                                                                               | X |   | summary\summary.pdf, pages 49-53.                                                                           |
| 12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic) | X |   | crt                                                                                                         |
| 13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)                    | X |   | crf                                                                                                         |

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY<sup>b,d,e</sup>

|                                                                                           | Y | N | COMMENTS<br>(If paper: list volume & page numbers)<br>(If electronic: list folder & page numbers) |
|-------------------------------------------------------------------------------------------|---|---|---------------------------------------------------------------------------------------------------|
| 1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits | X |   | summary\summary.pdf, pages 40-48.                                                                 |
| 2. Summary of Each Technical Section                                                      | X |   |                                                                                                   |
| a. Chemistry, Manufacturing, & Controls (CMC)                                             | X |   | summary\summary.pdf, pages 54-60.                                                                 |
| b. Nonclinical Pharmacology/Toxicology                                                    | X |   | summary\summary.pdf, pages 61-89.                                                                 |
| c. Human Pharmacokinetic & Bioavailability                                                | X |   | summary\summary.pdf, pages 90-109.                                                                |
| d. Microbiology                                                                           |   | X | Not applicable.                                                                                   |
| e. Clinical Data & Results of Statistical Analysis                                        | X |   | summary\summary.pdf, pages 111-228.                                                               |

|                                                                             |   |                                                                |
|-----------------------------------------------------------------------------|---|----------------------------------------------------------------|
| 3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies | X | summary\summary.pdf, pages 310-323.                            |
| 4. Summary of Safety                                                        | X | summary\summary.pdf, pages 229-309.                            |
| 5. Summary of Efficacy                                                      | X | Summary\summary.pdf, pages 165-166 (in Clinical Data Summary). |

Y = Yes (Present), N = No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS<sup>c,d,e</sup>

|                                                                                                                                                                                    | Y | N | COMMENTS<br>(If paper: list volume & page numbers)<br>(If electronic: list folder & page numbers)                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. List of Investigators                                                                                                                                                           | X |   | clinstat\8.1listinvest.pdf, pages 1-35.                                                                                                                                                                                                                                                          |
| 2. Controlled Clinical Studies                                                                                                                                                     | X |   |                                                                                                                                                                                                                                                                                                  |
| a. Table of all studies                                                                                                                                                            | X |   | summary\summary.pdf, pages 120-124.<br>clinstat\ise\ise.pdf, pages 17-21.                                                                                                                                                                                                                        |
| b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies) | X |   | <u>Prevention studies:</u> 1998005, 19998006, 171, 183<br><u>Treatment studies:</u> 1997092, 1997095<br>(clinstat\8.4wllcntrlclintrls.pdf)<br><br><u>Labeling comprehension study</u><br><u>Consumer usage studies:</u> 1998003, 1998067, 1998014, 1997091.<br>(clinstat\8.5uncntrlclintrls.pdf) |
| c. Optional overall summary & evaluation of data from controlled clinical studies                                                                                                  |   | X |                                                                                                                                                                                                                                                                                                  |
| 3. Integrated Summary of Efficacy (ISE)                                                                                                                                            | X |   | clinstat\ise\ise.pdf, pages 1-911.                                                                                                                                                                                                                                                               |
| 4. Integrated Summary of Safety (ISS)                                                                                                                                              | X |   | clinstat\iss\iss.pdf, pages 1-1600.                                                                                                                                                                                                                                                              |

|                                                       |   |  |                                                                                                   |
|-------------------------------------------------------|---|--|---------------------------------------------------------------------------------------------------|
| 5. Drug Abuse & Overdosage Information                | X |  | clinstat\8.9drgabuse.pdf, pages 1-67.                                                             |
| 6. Integrated Summary of Benefits & Risks of the Drug | X |  | clinstat\riskben\riskben.pdf, pages 1-23.                                                         |
| 7. Gender/Race/Age Safety & Efficacy Analysis Studies | X |  | clinstat\ise\ise.pdf, pages 44-49, 78-85 (prevention studies); pages 123-130 (treatment studies). |

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS<sup>d,e</sup>

|                                                                                                                                                                                                                                                       | Y | N | COMMENTS<br>(list volume & page numbers)<br>(If electronic: list folder & page numbers) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|-----------------------------------------------------------------------------------------|
| 1. [ ]                                                                                                                                                                                                                                                | X |   |                                                                                         |
| 2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.) | X |   | A paper copy of the application summary and each technical section is provided.         |
| a. Proposed unannotated labeling in MS WORD                                                                                                                                                                                                           | X |   | Provided on diskette.                                                                   |
| b. Stability data in SAS data set format (only if paper submission)                                                                                                                                                                                   |   | X |                                                                                         |
| c. Efficacy data in SAS data set format (only if paper submission)                                                                                                                                                                                    | X |   | Provided on CD-ROM.                                                                     |
| d. Biopharmacological information & study summaries in MS WORD (only if paper submission)                                                                                                                                                             |   | X |                                                                                         |
| e. Animal tumorigenicity study data in SAS data set format (only if paper submission)                                                                                                                                                                 |   | X | No carcinogenicity studies conducted with this omeprazole salt.                         |

|                         |   |  |
|-------------------------|---|--|
| 3. User-fee cover sheet | X |  |
|-------------------------|---|--|

Y=Yes (Present), N=No (Absent)

<sup>a</sup>"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

<sup>b</sup>"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

<sup>c</sup>"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

<sup>d</sup>"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

<sup>e</sup>"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

### Conclusions

No filing issues from an administrative standpoint.

[ 151 ] 3/1/00  
 Maria R. Walsh, MS  
 Regulatory Project Manager

cc:

Original NDA 21-229  
 HFD-180/Div. Files  
 HFD-180/PM/M. Walsh  
 HFD-180/L. Talarico  
     H. Gallo-Torres  
     J. Choudary  
     L. Zhou  
 HFD-180/Reviewers  
 final: M. Walsh 3/1/00

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ADMINISTRATIVE REVIEW

NDA 21-229

FEB 16 2000

The Proctor and Gamble Co.  
Attention: William Kozarek, Ph.D.  
8700 Mason-Montgomery Road  
Mason, Ohio 45040-9462

Dear Dr. Kozarek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Prilosec 1 (omeprazole magnesium) Tablets

Therapeutic Classification: Standard (S)

Date of Application: January 27, 2000

Date of Receipt: January 27, 2000

Our Reference Number: NDA 21-229

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 27, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 27, 2000 and the secondary user fee goal date will be January 27, 2001.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 443-8017.

Sincerely,

[ /S/ ] 2-16-00

Maria R. Walsh, M.S.  
Regulatory Project Manager  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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NDA 21-229

Page 3

cc:

Archival NDA 21-229

HFD-180/Div. Files:

HFD-180/M. Walsh

DISTRICT OFFICE

final: M. Walsh 2/16/00

filename: 21229.Feb-2000.ACK.doc

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY  
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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** June.3, 1999  
**Time:** 10:00 am - 12:00 pm  
**Location:** Parklawn Building, Conference Room 6B-45

**Application:** IND 23,284  
Prilosec (omeprazole) Delayed-Release Capsules

**Sponsor:** Astra Pharmaceuticals, L.P.

**Type of Meeting:** Pre-NDA; CMC issues for Omeprazole Magnesium (MUPS) Tablets

**Meeting Chair:** Eric Duffy, Ph.D., Chemistry Team Leader

**Meeting Recorder:** Maria R. Walsh, M.S., Regulatory Project Manager

### FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)  
Eric Duffy, Ph.D., Chemistry Leader  
Arthur Shaw, Ph.D., Chemistry Reviewer  
Maria R. Walsh, M.S., Regulatory Project Manager

### Sponsor Attendees:

Astra Pharmaceuticals, L.P.  
Gary Horowitz, Ph.D., Regulatory Liaison Director  
Kathy Monday, Executive Director, Product Operations  
Suzanne Mullins, Director, Product Development  
Beth Kendersky, CMC Product Operations Manager  
George A. Kummeth, Regulatory Project Manager

### Astra Hässle AB

Pontus Bergstrand, M.S., Associate Director, Pharmaceutical Project Management  
Martin Wikberg, Ph.D., Associate Director, Pharmaceutical Technology Solids  
Magnus Erickson, Ph.D., Director, Substance Analysis  
Dick Johansson, M.S., Associate Director, Pharmaceutical Project Management

**Background:** Astra Pharmaceuticals, L.P. and The Proctor & Gamble Company are pursuing the development of omeprazole magnesium tablets, under IND 54,307, for two over-the-counter (OTC) indications: the relief of and the prevention of heartburn, indigestion, and sour stomach. Astra Pharmaceuticals, L.P. requested this meeting to discuss the Chemistry, Manufacturing, and Controls (CMC) section of a future NDA for omeprazole magnesium tablets. A meeting package, dated April 26, 1999, was submitted to the Division of Gastrointestinal and Coagulation Drug Products under [redacted] for Prilosec (omeprazole) Delayed-Release Capsules for purposes of protecting the confidentiality of the CMC information

**Meeting Objectives:** To discuss questions raised by the sponsor in the April 26, 1999 meeting package.

**Agenda Item 1: General Discussion**

Clinical program: The sponsor presented a brief overview of the clinical program which consists of six pivotal efficacy studies, a label comprehension study, and two Actual Use studies.

[redacted]; The sponsor confirmed that drug substance [redacted] was used to manufacture the drug product for use in the clinical studies and that drug substance [redacted] will be used to manufacture the commercial drug product.

The FDA indicated that the IVIVC study is critical in demonstrating the equivalence of the two drug substance manufacturing processes. The sponsor said the drug substance made from the two processes are identical and no in-vivo studies would be conducted to demonstrate equivalence.

The sponsor explained that [redacted] does not include [redacted] in the final [redacted] step whereas [redacted] does. The sponsor indicated that a comparison of the specifications, impurity profiles, and the physical and chemical characteristics of the two drug substances demonstrates that they are indistinguishable. The sponsor said particle size was not addressed in the comparison as [redacted] is performed in the first step of the manufacture of drug product.

The FDA inquired how drug substance manufactured by [redacted] will be compared. The sponsor said comparisons will include physical and chemical characteristics. In addition, comparisons of dissolution profiles, impurity profiles, release specifications, and stability data between drug product manufactured using either [redacted] or [redacted] drug substance will be performed.

The sponsor indicated that there is one [redacted] the magnesium salt confirmed through [redacted] data.

Slow Dissolution Batches: The FDA noted that some batches of drug product manufactured with [redacted] drug substance exhibited slow dissolution. How is this to be correlated with the more rapidly dissolving drug product to be marketed? The sponsor confirmed that no slow dissolution batches were used in the clinical trials. This information will be clearly stated in the NDA. The sponsor said the slow dissolution batches are used for the European market. (MUPS tablets are approved in 18 European countries and marketed in 10).

The sponsor confirmed that the slow dissolution batches did not fail release specifications but had dissolutions close to the lower end of the specification range. The sponsor indicated that multipoint dissolution data are collected for all stability batches and agreed to include this data in the NDA. The sponsor indicated that the dissolution profiles of the batches used in the clinical studies will be included in the DMF but that the dissolution profile is not a specification.

The sponsor said that during investigation of the batches that exhibited slow dissolution rates, it was noted that raising the pH of the \_\_\_\_\_ from \_\_\_\_\_ achieved normal dissolution rates. The FDA pointed out that the IVIVC report does not include this information regarding the relationship of pH and different dissolution rates. The sponsor agreed to include this information in the report.

The sponsor added that even after pH adjustment was introduced into production, a few batches still exhibited slow dissolution rates. This was corrected through the addition of an \_\_\_\_\_ in the drug substance manufacturing process. The FDA questioned whether the \_\_\_\_\_ removes \_\_\_\_\_ and the sponsor replied that it could remove \_\_\_\_\_ impurities. The FDA inquired whether any \_\_\_\_\_ is present in the drug substance. The sponsor confirmed a \_\_\_\_\_ of approximately \_\_\_\_\_ and added that no differences were seen between \_\_\_\_\_ and \_\_\_\_\_ material.

The sponsor said that \_\_\_\_\_ batches were recently produced using \_\_\_\_\_ drug substance and no dissolution problems were observed. The FDA requested inclusion of the dissolution data from these batches in the NDA.

**DMF Submissions:** In response to the FDA's inquiry whether the current Drug Master Files (DMFs) for the drug substance and drug product will be amended to include the new manufacturing process, the sponsor proposed to close the current DMFs and submit two new DMFs plus a third DMF to add \_\_\_\_\_ as a supplier of drug substance. The sponsor confirmed that \_\_\_\_\_ and \_\_\_\_\_ will be the suppliers of drug substance. After some discussion, it was agreed that the sponsor will amend the two current DMFs and submit a new DMF to add \_\_\_\_\_ as a supplier of drug substance.

**Packaging:** The FDA confirmed that the packaging information ( \_\_\_\_\_ as packager) may be submitted in the NDA rather than in a new DMF.

The sponsor confirmed that the OTC packages will be blisters and pouches for physician samples. The sponsor confirmed that the blisters will be child resistant but it was unclear whether the pouches would be child resistant. The FDA recommended the sponsor contact the Consumer Product Safety Commission (CPSC) to clarify whether child resistant

packaging is required for physician samples.

**Starting Material:** The FDA clarified that [redacted], referred to as the [redacted] for omeprazole magnesium in the meeting package under section 2.1.1., implies that it is not manufactured under Good Manufacturing Practices (GMP). The sponsor agreed not to refer to [redacted] as [redacted] and added that the NDA will contain a schematic process.

**Agenda Item 2: Sponsor's Questions**

**A. Drug Substance Stability**

In the NDA, we will provide — months stability data on three batches of omeprazole magnesium synthesized at — by — and 12 months stability data on three batches of omeprazole magnesium synthesized at — by —

Furthermore, we will provide — months stability data on three lots of — drug substance, — and — months stability data on one lot of — drug substance. — We will also provide a commitment to amend the NDA during the review period with up to — months of stability data on these batches.

**FDA Response: (provided in writing at the meeting)**

- 1) Your stability proposals are acceptable.
- 2) The expiration date is based upon the length of real time data submitted plus — months. Use of the proposed additional stability data in determining the expiration date will depend upon when this data is submitted during the NDA review period.
- 3) The NDA should include information regarding the levels of impurities and how they vary with pH.
- 4) Regarding DMF — Provide the experimental evidence for the creation of the degradation products (i.e. experimental procedure for creating the degradation products, structure proof, chromatographic behavior) and a comparison with the known degradation products for omeprazole.
- 5) Regarding the new synthetic procedure: Provide evidence to show the comparability of the degradation profile of the drug substance.

**Discussion:**

Submission of additional stability data: The sponsor inquired when the additional stability data would be needed for review. The FDA explained that since this NDA would be a standard review with a primary goal date of \_\_\_\_\_ months from the date of receipt (secondary goal date - \_\_\_\_\_ months), the chemistry review would be finished in about \_\_\_\_\_ months. The submission of the stability data would not be considered a major amendment (with extension of the goal date). Therefore, whether the data can be reviewed in the first review cycle will depend upon when it is submitted in relationship to the \_\_\_\_\_-month chemistry review time.

Retest data: The sponsor said the retest period for drug substance is \_\_\_\_\_. The FDA said it is possible to have different retest dates for the drug substance manufacturing sites but the data will need to be reviewed.

Expiration date: The FDA said a stability protocol could be developed for extension of expiry. It was noted that stability data exists on \_\_\_\_\_ lots of the 10 mg strength and \_\_\_\_\_ lot of the 20 mg strength all manufactured from \_\_\_\_\_ drug substance. The sponsor confirmed that only the 20 mg strength will be marketed. In addition, the sponsor confirmed that the \_\_\_\_\_ lots of the 10 mg strength were \_\_\_\_\_ batches whereas the \_\_\_\_\_ lot of the 20 mg was a \_\_\_\_\_ batch.

The sponsor described the manufacturing differences between the two dosage strengths. The major difference is the \_\_\_\_\_  
\_\_\_\_\_. In addition, the amount of enteric coating ingredients differs to achieve the same coating thickness.

The FDA said assignment of the expiry date is based upon data from \_\_\_\_\_ batches of a dosage strength. In this case, only \_\_\_\_\_ batch of the 20 mg strength is available and it is unclear at this time, based on the manufacturing differences, whether the batches of both strengths can be pooled for statistical analysis. In addition, assignment of the expiry date is not usually based on \_\_\_\_\_ batches. The FDA said the sponsor should justify the use of stability data from \_\_\_\_\_ batches.

In-process controls/Scale-up and controls: The sponsor described the in-process controls of the coating process and confirmed that \_\_\_\_\_ analysis is performed during the \_\_\_\_\_ stage to check for \_\_\_\_\_. The FDA requested that a description of how the control of \_\_\_\_\_ is performed be included in the process description in the DMF.

With regard to scale-up and controls, the sponsor said robustness testing is used to identify critical process parameters. The sponsor clarified that in addition to test of \_\_\_\_\_ the quality of the \_\_\_\_\_ is tested as part of the robustness testing. The FDA requested



- 5) Regarding DMF — Provide data to justify not performing the test for omeprazole release at the acid stage.

**Discussion:**

Assay: The FDA noted that there is no data on — testing. It is understood that omeprazole degrades in — but only measuring what remains is not satisfactory. The FDA requested that the sponsor develop an — assay to measure — products. The sponsor explained that it would be extremely difficult to measure omeprazole and its cascade of degradants which are formed in — and to quantify them. The FDA said the sponsor should then address in the DMF why an — assay is not feasible and include details of all experiments performed.

**Agenda Item 3: Additional Discussion**

Enantiomers: The FDA said a guidance is under development to address chirality. It was noted that omeprazole magnesium is optically active but there is currently no test for optical activity. The FDA requested that the sponsor develop a method to differentiate between the racemic and enantiomer forms of omeprazole magnesium in both the drug substance and drug product.

Hold Times: The FDA requested that a description of and justification for hold times of the ( — ) be included in the DMF. Expiry dating is begun when omeprazole magnesium meets hydroxypropyl methylcellulose. If extended hold times are requested, appropriate data must be provided in a prior approval supplement. An alternative approach is to provide stability data on — batches held at maximum hold times at each stage.

Batch Records: The FDA said that representative master and executed batch records should be provided in the DMF.

Pre-approval Inspections: The FDA said that all manufacturing facilities must be ready for inspection at the time of NDA submission. A separate list of all manufacturing and packaging sites and addresses was requested.

Non-Compendial Materials: The sponsor raised the issue of using non-compendial materials (C — ) in the MUPS tablet formulation and presented a comparison of the current testing based on EP and USP specifications. The FDA said this issue needs to be reviewed before commenting.

Miscellaneous: The sponsor confirmed that there is no USP monograph for omeprazole magnesium.

The FDA requested that a justification for the selected dissolution specification (Q value)

be included in the DMF.

The FDA requested that drug product release specifications be provided in the NDA.

The FDA said that Letters of Authorization (LOAs) must be current and specific for each material including each component of the blister and pouch packages.

APPEARS THIS WAY  
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