

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **019810/S036**

Trade Name **PRILOSEC Delayed Release Capsules**

Generic Name **Omeprazole**

Sponsor **Astra Merck, Inc.**

NDA 19-810/S-036

Walsen
NOV 26 1996

Astra Merck Inc.
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your May 4, 1995 supplemental new drug application and your resubmission dated December 27, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your amendments dated May 15 and 22, 1995 and April 8 and 10, August 7, September 20, and October 21, 1996.

The supplemental application provides for a new indication: treatment of symptomatic gastroesophageal reflux disease (GERD).

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the enclosed marked-up draft labeling. In addition, all previous revisions as reflected in the most recently approved package insert must be included.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-810/S-036. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

NDA 19-810/S-036

Page 2

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Maria R. Walsh, M.S.
Regulatory Health Project Manager
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director -
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

**PATENT INFORMATION FOR OMEPRAZOLE
(PRIOSEC®) - APPLICATION NUMBER 19810 001**

- | | |
|--|--------------------------------|
| 1. Applicant | Astra Merck Inc. |
| 2. Patent No. | 4,786,505 |
| Expiration Date | April 20, 2007 |
| 3. Type of Patent | Drug product and method of use |
| 4. Name of the Patent Owner | Aktiebolaget Hässle |
| 5. Representative authorized to receive notice of patent certification under sections 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.52 and 314.95 | Astra Merck Inc. |

DECLARATION

The undersigned declares that Patent No. 4,786,505 covers the formulation, composition, and method of use, i.e., Short-Term Treatment of Active Duodenal Ulcer, Gastroesophageal Reflux Disease (GERD), Severe Erosive Esophagitis, Poorly Responsive Symptomatic GERD, Pathological Hypersecretory Conditions and Maintenance of Healing of Erosive Esophagitis, of omeprazole (PRLOSEC[®]). This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.



Elliott T. Berger, Ph.D.

Executive Director, Regulatory Affairs
Astra Merck Inc.


**PATENT INFORMATION FOR OMEPRAZOLE
(PRIOSEC[®]) - APPLICATION NUMBER 19810 001**

- | | |
|--|--------------------------------|
| 1. Applicant | Astra Merck Inc. |
| 2. Patent No. | 4,853,230 |
| Expiration Date | April 20, 2007* |
| 3. Type of Patent | Drug product and method of use |
| 4. Name of the Patent Owner | Aktiebolaget Hässle |
| 5. Representative authorized to receive notice of patent certification under sections 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.52 and 314.95 | Astra Merck Inc. |

* By terminal disclaimer.

DECLARATION

The undersigned declares that Patent No. 4,853,230 covers the formulation, composition, and method of use, i.e., Short-Term Treatment of Active Duodenal Ulcer, Gastroesophageal Reflux Disease (GERD), Severe Erosive Esophagitis, Poorly Responsive Symptomatic GERD, Pathological Hypersecretory Conditions and Maintenance of Healing of Erosive Esophagitis, of omeprazole (PRLOSEC®). This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.



Elliott T. Berger, Ph.D.
Executive Director, Regulatory Affairs
Astra Merck Inc.

**PATENT INFORMATION FOR OMEPRAZOLE
(PRILOSEC®) - APPLICATION NUMBER 19810 001**

1. **Applicant** Astra Merck Inc.
2. **Patent No.** 4,255,431
Expiration Date April 5, 2001
3. **Type of Patent** Drug substance, drug
product and method of use
4. **Name of the Patent Owner** Astra Aktiebolag
5. **Representative authorized to
receive notice of patent
certification under sections
505(b)(3) and (j)(2)(B) of the
Federal Food, Drug, and
Cosmetic Act and 21 C.F.R.
§§ 314.52 and 314.95** Astra Merck Inc.

DECLARATION

The undersigned declares that Patent No. 4,255,431 covers the formulation, composition, and method of use, i.e., Short-Term Treatment of Active Duodenal Ulcer, Gastroesophageal Reflux Disease (GERD), Severe Erosive Esophagitis, Poorly Responsive Symptomatic GERD, Pathological Hypersecretory Conditions and Maintenance of Healing of Erosive Esophagitis, of omeprazole (PRILOSEC[®]). This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.



Elliott T. Berger, Ph.D.
Executive Director, Regulatory Affairs
Astra Merck Inc.

EXCLUSIVITY SUMMARY for NDA # 19-810 SUPPL # 036

Trade Name PRILASEC Generic Name OMEPRAZOLE
Applicant Name ASTRA MEPCO HFD-180

Approval Date 11/20/96

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 / / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

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

SE1

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 / / 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 / / NO / /

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 # 19-510 FRILCSEC (OMEPRAZOLE) DELAYED-RELEASE CAPSULES

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 8. 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 / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / / 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 8:

- (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 / / 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 / /

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 / /

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 # I-1601a

Investigation #2, Study # _____

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 T-16C1a	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

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 T-16C1a	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

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 # I-1601a

Investigation #_, Study # _____

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 I-1601a !

IND # _____ YES / / ! NO / ✓ / ! Explain: _____

Investigation #2 !

IND # _____ YES / / ! 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 I-1601a !

YES / / Explain _____ ! NO / ✓ / ! Explain Astra Hässle conducted

Study I-1601a. Astra Hässle is a subsidiary of Astra AB. Astra AB is the parent company of Astra Merck, sponsor of this supplement (i.e. Astra AB owns 50% of Astra Merck).

Investigation #2

YES / / Explain _____ ! NO / / Explain _____

- (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 / /

If yes, explain: _____

Maria Walsh 11/21/96
 Signature Date
 Title: Project Manager

[Signature] 11/28/96
 Signature of Division Director Date

Original NDA

Division File

HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-810/SEI-036 Trade (generic) names PRILOSEC (OMEPRAZOLE)
DELAYED-RELEASE CAPSULES

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

1/13/96
JUN 13 1996

MEDICAL OFFICER'S REVIEW

NDA 19-810/S-036

PRILOSEC® Delayed-Release Capsules

Supplemental New Drug Application

for the

Treatment of Symptomatic GERD

20 mg once-a-day for 4 to 8 weeks

Submitted by Astra Merck, PA

Reviewer:

Hugo E. Gallo-Torres, M.D., Ph.D.

HFD-180

NDA 19-810/S-036

Page 2

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 19-810
S/036

Date Submitted: December 27, 1995

Sponsor: Astra Merck
Wayne, PA

Drug: PRILOSEC® (omeprazole=OME)
Delayed Release Capsules

Route of Administration: Oral

Proposed Indication: Treatment of Symptomatic GERD

First Draft to Superior: May 8, 1996

Review Completed: June 12, 1996

Material Reviewed: Clinical Data Section (Item 8), Including
Vol. 1: Cover letter, Proposed text of
labeling
Vol. 3: Summary, Synopsis
Vol. 4: Supportive Study Documents
Vol. 5: CR Tabulations
Vol. 6,7: Sites/Investigators
Vol. 8: CRFs

MEDICAL OFFICER'S REVIEW OF NDA 19-810/S-036

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I. BACKGROUND/INTRODUCTION

The subject of this NDA Supplement is PRILOSEC® (omeprazole=OME), a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of H⁺/K⁺-ATPase enzyme system. OME blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. PRILOSEC Delayed-Release Capsules contain an enteric coated granule formulation of OME (because this compound is acid-labile) so that absorption of OME begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of OME occurring within 0.5 to 3.5h. Peak plasma concentrations of OME and AUC are ca. proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to I.V. administration) is about 30 to 40% at doses of 20-40 mg due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1h and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%. The bioavailability of OME increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules. OME has definite effects on gastrin secretion but whether it affects the secretion (locally) of other peptides is not known. The effects on gastrin may be related to ECL-cell hyperplasia but - in man - not pronounced effects on the parameters upon short-term (up to 12 weeks) administration, as is being proposed for the present indication, is expected.¹

Of the pharmacodynamic properties needed for beneficial effects on symptomatic GERD, it has already been mentioned that OME is a very effective antisecretory. OME has been shown not to affect esophageal peristalsis or LES pressure (J. Dent et al., *Gastroenterology* 88:1363 (1985); T.K. Chakraborty et al., *Aliment. Pharmacol. Therap.* 1:627-631 (1987)]. Whether OME has effect on gastric emptying appears controversial. A previous study indicated that OME had no effect on gastric emptying in patients with DU disease [M. Horowitz et al., *Br. J. Pharmacol.* 18:791-794 (1984)]. A more recent publication reports that OME, 40 mg [twice the dose being proposed for the Tx of symptomatic GERD], markedly delays gastric emptying of a digestible solid meal [L. Benni et al., *Gut* 35(Suppl. 5):S48 (1994)].² Finally, it is of interest to mention that OME has in-vitro³ antimicrobial activity [S. Sauerbaum et al., *Eur. J. Clin. Microbiol. Infect. Dis.* 10:92-93 (1991)], by a mechanism of action that

¹OME only slightly reduces pepsinogen secretion [T. Lind et al., *Gut* 24:270-276 (1983); T. Lund et al., *Scand. J. Gastroenterol.* 21:1004-1010 (1986)] but peptic activity is markedly reduced by this drug because pepsinogen is largely biologically inactive at the levels of pH that OME produces. OME has been shown not to affect secretion of IF by parietal cell.

²This finding may be more relevant to the use of OME in DU patients, in whom a fast gastric emptying may increase the duodenal ulcer load, and, conversely, in dyspeptic patients, in whom gastric emptying is often delayed.

³The MIC₅₀ for OME is ca. 50 to 128 mg/L. Activation of the benzimidazole appears essential for antibacterial action. Acidic conditions generally increase this activity. The activity at neutral pH appears to parallel the ease with which the benzimidazole is activated by protons.

is not entirely clear. But long-term eradication of H. Pylori, even with OME 40 mg b.i.d. does not result. HP eradication is achieved by combining OME with antibiotics.

By now, OME has been approved for the S-T Tx of DU and GU, erosive esophagitis, poorly responsive symptomatic GERD⁴, pathological hypersecretory conditions and more recently, maintenance of healing of erosive esophagitis.

The sponsor is now pursuing a new indication: Tx of symptomatic GERD (Tx of patients that have no endoscopic evidence of esophagitis, only symptoms of GERD). This is an important clinical entity as almost half of the patients with reflux symptoms (e.g. heartburn) have no endoscopic evidence of esophagitis [T. Havelund et al., Scand. J. Gastroenterol. 22(Suppl. 201):69-73 (1994)] and for these patients the resolution of symptoms is the sole measure of outcome. FDA-approved treatments for this specific indication include the use of a) Zantac[®] (ranitidine) at the recommended oral dosage of 150 mg b.i.d.; b) Pepcid[®] (famotidine) at the recommended oral dosage of 20 mg b.i.d. and c) Reglan[®] (metoclopramide) at the recommended oral dose of 10 to 15 mg up to q.i.d.. Also approved is the use of PROPULSID (cisapride), for the symptomatic Tx of patients with nocturnal heartburn due to GERD, at oral doses of 10 to 20 mg q.i.d.. No other H₂-receptor antagonist is presently approved for this indication. But the treatment/control of symptoms of GERD is included as part of the indication: treatment of endoscopically-diagnosed esophagitis for a number of drugs, such as a) Tagamet[®] (cimetidine) at the recommended oral dosage of 1600 mg daily in divided doses (800 mg b.i.d. or 400 mg q.i.d.); b) ZANTAC[®] (ranitidine) at the recommended oral dosage of 150 mg q.i.d.; c) Axid[®] (nizatidine), at the recommended oral dose of 150 mg b.i.d.; d) Pepcid[®] (famotidine), at the recommended oral dose of 20 to 40 mg b.i.d.; e) Prevacid[®] (lansoprazole) at the recommended oral dose of 30 mg once a day; and f) Reglan[®] (MCP) at the oral dose of 15 mg q.i.d.. The H₂-receptor antagonists, MCP and the PPIs can be used for up to 12 weeks. Interestingly, the word symptoms is not included in the approved indication of OME for the S-T Tx of erosive esophagitis. The other GERD indication for OME reads: S-T Tx (4-8 weeks) of symptomatic gastroesophageal reflux disease (esophagitis) poorly responsive.... It is also of interest to mention that ca. half of the patients with frequent and severe heartburn, including those with severe esophagitis can be successfully self-treated with currently available OTC drugs (i.e. antacids and H₂-receptor antagonists at doses lower than those specified above).

In addition to the above-described approved drugs for the Tx of GERD, the scientific literature describes the experimental use of sucralfate, domperidone, bethanecol (and cimetidine CR).

Through the present supplemental application the sponsor is requesting a change in the INDICATIONS & USAGE section of the prescribing information for

⁴PRIOLOSEC[®] was approved for the second-line Tx of symptomatic GERD (i.e. symptomatic GERD poorly responsive to histamine H₂-receptor antagonists), rather than first time Tx of symptomatic GERD mainly because of safety concerns. At the time of approval, efficacy data was not required in the poorly responsive patient population.

PRILOSEC®. Among other indications, PRILOSEC® is currently indicated for the S-T Tx of "symptomatic gastroesophageal reflux disease (esophagitis) poorly responsive to customary medical treatment, usually including an adequate course of a histamine H₂-receptor antagonist". The sponsor is requesting that this claim be changed to indicate that PRILOSEC® can be used as a "first-line" therapy for symptomatic GERD, without regard to a patient's response to previous therapy.

The sponsor's initial approach was to add to the above a new indication S-T treatment of (as first line Tx) while retaining the second line indication for GERD. Supplement -036 was refused for filing under 21 CFR 314.101(d) on June 8, 1995 because results of two adequate and well controlled studies in support of the second-line indication for the Tx of poorly responsive symptomatic GERD were not included in the submission. At an August 14, 1995 informal conference to discuss refusal to file, the recommendation was made to the sponsor to resubmit supplement -036 with reference to the original NDA studies and the results of a new dose-response study demonstrating that 20 mg is the best dose of OME for both erosive and non-erosive GERD patient populations. They were told to delete from the labeling all references to the second-line indication (which had never been supported by results of two adequate and well-controlled studies in this specific patient population).

In support of this revised indication the sponsor submits data derived from Astra Hässle study I-1601a, comparing the efficacy of OME at daily doses of 20 mg and 10 mg to PL in patients treated for 4 weeks for the symptoms of GERD in the absence of erosive esophagitis. In addition to these clinical efficacy data, the study design for protocol I-1601a included a 24-hour pH monitoring to further describe the effect of OME on patients with pathologic GER. For this secondary efficacy parameter, the sponsor reanalyzed the primary efficacy variable in those patients who had pH values <4 in the distal esophagus for at least 4% of the pH monitoring time. This information is important to assess if the Tx level of esophageal acid exposure predicts the response of symptoms to Tx with different doses of OME.

After assessment of the evidence the reviewer expects to be able to answer the following questions related to the treatment of symptomatic GERD and the sponsor's proposed changes in the labeling.

1. Do the study results demonstrate efficacy?
2. Can a treatment dose (10 vs 20 mg OME) be identified and recommended?
3. Are there safety concerns for the short-term use of OME in this patient population?
4. What are the recommended changes in the labeling?

Answers to questions 1. through 3. are included under the Comments section of this review. Answer to question 4. is included under Recommendations for Regulatory Action.

II. STUDY PROTOCOL I-1601a

"Omeprazole in the management of patients with gastroesophageal reflux symptoms without macroscopic esophagitis"

A multicenter study in Scandinavia

Study period: March 1993-September 1994

1. Objectives

Primary objective:

- to compare, at the 4 weeks visit, the efficacy of OME 20 mg, OME 20 mg and PL on the relief of heartburn (HB) in the Tx of patients with HB as the predominant reflux symptom but without macroscopic esophagitis.

Secondary objectives:

- to evaluate the pre-Tx level of esophageal acid exposure as a prognostic factor in the relief of HB,
- to evaluate Quality of Life with the primary aim to investigate whether there are differences between the Tx groups with regard to general well-being and subjective symptoms. [NOTE: This part of the study is not evaluated. QOL analyses may not be useful since a validated scale is not currently available].

The summary protocol that follows includes appropriately documented amendments (none major).

2. Study Population (Table 1)

This Table lists the inclusion/exclusion criteria. These were adequate for the intended purpose of the trial. It is to be noted that the results of the 24-h pH monitoring were not used as a selection criteria for inclusion in the trial. These data were used only as an explanatory variable (secondary objective) in the analysis of the results.

TABLE 1
Study I-1601a

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
<p> M or F >18 years of age Hx of HB as the predominant symptom at least during the last 12 mo. plus Episodes of HB occurring on at least 2 days during the last 7 days. Signed or witnessed verbal informed consent </p>	<p> Presence or Hx of macroscopic erosive and/or ulcerative esophagitis and/or DU or GU. Esophageal stricture and/or Barrett's esophagus. Symptoms indicating complications of GERD (e.g. melena, hematemesis). Hx of esophagogastric surgery except for simple closure of perforations. Concurrent disease (past or present) likely to complicate the evaluation of test med., e.g. significant cardiovascular, renal or hepatic disease, or malignancy. Clinically significant abnormal values in the pre-study laboratory screen as judged by the investigator, other than those directly related to some concurrent and stable disease. Tx with any investigational compound within the previous month. Tx with antisecretory agents (e.g. H₂-receptor antagonists or PPIs) in ulcer healing doses within the month prior to endoscopy. Pregnancy or lactation. Alcohol or drug abuse or any conditions associated with poor compliance. Previous enrolment in the study. Requirement of an interpreter. </p>
<p>a) In the protocol no clarification was given about the meaning of "significant" cardiovascular, renal or hepatic disease.</p>	

3. Test Medication

a. Test Medications

- OME 20 mg (LOSEC®) and OME 10 mg capsules were used and dispensed as enteric-coated pellets in hard gelatin capsules.⁵ PL capsules, formulated as non-pareil pellets and antacid tablets (Novalucol Novum/Balancid Novum)⁶ were used.

b. Blinding Procedure/Packing/Dispensing/Compliance

These were all adequate.

- The study centers were provided with individually sealed envelopes containing the treatment code for each patient. These envelopes were returned to Astra at the completion of the study. The code for an individual patient was only broken if knowledge of the administered drug was necessary for treating an emergency.
 - During the first two weeks all patients received one bottle containing either 25 OME 20 mg, 10 mg or PL capsules.
 - During weeks 3-4 the patients received another bottle containing 25 OME 20 mg, 10 mg or PL capsules.
 - At each visit patients were also provided with blister packs containing 30 tablets Novalucol Novum/Balancid Novum as additional therapy.
- The drugs were dispatched from Astra Hässle AB to the local Astra companies in the participating countries, whereafter the drugs were dispatched directly to the investigators. Drug packs and unused medication were collected and compliance was checked by the investigator or his/her delegate by counting any remaining capsules and/or tablets. The responsibility of drug disposal of remaining medication was delegated to the hospital pharmacy by the local Astra monitor.

⁵The OME capsules were produced by Astra Pharmaceutical Production AB, Sweden and packed in bottles by Astra Hässle AB, Sweden.

⁶The PL capsules and antacid tablets were produced by Astra Pharmaceutical Production AB, Sweden and packed in bottles by Astra Hässle AB, Sweden.

- The batch numbers used in the study were:

Omeprazole 20 mg capsules	H431-13-5-2, H431-13-5-3
Omeprazole 10 mg capsules	H499-15-3-1
Placebo	H459-6-3-1, H459-6-3-2
Novalucol Novum	H779-2-1-2, H779-2-1-7, H779-2-1-9

c. Outcome of Tx Allocation

In their Table 2 (page 8-00049) the sponsor presented the number of patients assigned to each of the 27 participating centers and the randomization numbers finally assigned to each center. The following is noted:

- At pre-entry, patients were given an enrollment code which corresponded to a pre-printed number on the CRFs. A seven-digit randomization number was allocated to each patient on randomization to the study at visit 1. The center number 001-027 constituted the first three digits of the randomization number, i.e. patient No. 00200010 is patient number 10 at center number 2. At center 2 patient No. 0020005 was not used due to a delivery problem with the medication.
 - At center 7 patient Nos. 0070003-0070005 were not used because the study drugs were delivered in the wrong order from the pharmacy.
 - The sponsor decided to close centers 13 and 15 on August 30, 1993 and December 31, 1993, respectively, due to lack of patient recruitment.

4. Other Therapy

- Medication with antisecretory agents in healing doses for relief of acid-related symptoms was stopped one month before endoscopy. Other medication recommended in the Tx of acid-related symptoms; prokinetics (e.g. cisapride, domperidone, metoclopramide, bethanecol), sucralfate or anticholinergic agents, was stopped 7 days before 24h pH monitoring. Alginic acid and antacids were allowed to be taken up to the day of pH monitoring. During the study patients were only allowed to take those antacids dispensed by the investigator.
- Other medication which was considered necessary for the patient's welfare and which would not interfere with the test medication was allowed to be continued during the trial at the discretion of the investigator. Details of all medication given during the study and during the month prior to inclusion were reported in the CRF. Any changes in concomitant medication made during the study were also recorded in the CRF.

5. Clinical and Laboratory Assessments

Only those assessments related to HB and 24-h pH monitoring are briefly commented upon.

- Each patient's GERD history was recorded, including the duration of medication given during the last month.
- At inclusion in the study and at each visit the patients were questioned in a standardized way to assess the current severity and frequency of HB.
 - Frequency of HB was to be recorded as number of days with episodes during the last 7 days; none, 1 day, 2-4 days, 5-6 days or 7 days.

- Patients with Hx of HB as the predominant symptom and episodes of HB occurring on at least 2 days during the last 7 days prior to inclusion (visit 1) were enrolled in the study.

Heartburn: Substernal burning pain or discomfort associated either with oral radiation or worsened by meals, exercise or changed posture. Severity was classified as:

none: no symptoms
mild: awareness of sign or symptom, but easily tolerated
moderate: discomfort sufficient to cause interference with normal activities
severe: incapacitating, with inability to perform normal activities.

The patients were also questioned in a standardized manner "Does the study medication give sufficient control of your heartburn?"

- The endoscopy was performed within 21 days prior to inclusion. Patients with macroscopic erosive and/or ulcerative esophagitis were not eligible to enter the study. Macroscopic observations in the stomach and duodenum were also recorded.

- Other Specific Symptoms

Before inclusion to the study and at each visit, patients were questioned in a standardized manner to determine the current severity of regurgitation, dysphagia, epigastric pain and nausea. These symptoms were classified as:

none: no symptoms
mild: awareness of sign or symptom, but easily tolerated
moderate: discomfort sufficient to cause interference with normal activities.
severe: incapacitating, with inability to perform normal activities.

- Vomiting was recorded as absent or present.

- 24-hour pH Monitoring

Before trial medication was started, esophageal acid exposure was determined by 24-h pH monitoring and was performed within 14 days prior to inclusion. This 24-h ambulatory intra-esophageal pH-metry was performed with a glass or antimony electrode, placed 5 cm above the preferably manometrically localized LES. The 24-h pH monitoring was blinded to the investigator and the patient. The following variables were included:

- Number of reflux episodes (total, upright, supine)
- Total time pH <4 (min) (total, upright, supine)
- Percentage time pH <4 (%) (total, upright, supine)

Before the treatment code was broken, the abnormal esophageal acid exposure was defined as percentage of time with pH<4 for 4% or more of the 24-hour.

- The methods for collection, definitions, reporting, classification by seriousness and severity and overall terminology for AEs were all adequate.
- Also adequate were the reasons, listed below, to W/D patients from the trial:
 - Unacceptable AEs
 - Violation of Inclusion/Exclusion Criteria
 - Unwillingness to continue the trial
 - Non compliance with protocol.
- The procedures to be performed and recorded in the CRF in case of withdrawals, were adequate.

6. Statistical Methodology

a. Sample Size Determination

- The intended number of randomized patients was 500, in a 1:2:2 ratio for PL and each of the two OME arms.
- The sample size was determined under the assumption that Tx with OME 20 mg, OME 10 mg and PL would give a true rate of complete relief of HB of 85%, 70% and 40% respectively.
 - Using a 2-tailed test at an overall significance level of 5% (adjusted for three comparisons) give a power of 80% to detect a difference between OME 20 mg and OME 10 mg, a power of more than 90% to detect a difference between OME 10 mg and PL, and a power of more than 99% to detect a difference between OME 20 mg and PL.

b. Statistical Methods

- Proportions of complete relief of HB were compared by a Mantel-Haenszel Chi-square test stratified by center.
- The pre-Tx level of esophageal acid exposure as prognostic factor was evaluated using a logistic regression model with relief of HB as the dependent variable.

c. Types of Analyses Performed

- There were two different approaches to the analysis of the data, "All Patients Treated" (APT) and "Per Protocol" (PP).
- The APT approach attempts to address the question: "How does the drug work in patients prescribed the drug?".
 - According to the Study Protocol, patients not treated, patients receiving an unknown study drug and patients W/D due to baseline characteristics (e.g., abnormal result of baseline laboratory test) without assessment of efficacy were to be excluded from the APT analysis.
 - Patients who for other reasons had not had their HB symptoms determined at the 4 weeks visit were to be considered as Tx Fxs in the formal APT analysis of HB relief.
- The PP approach attempts to answer the question: "How effective is the drug in patients who take the drug as prescribed?".
- All patients excluded from the APT analysis were also to be excluded from the PP analysis.
- In the PP analysis all data affected by major protocol deviations were to be excluded.

7. Results

a. Participating Investigators/Number of Patients per Center

Listed in Table 2 are total number of patients enrolled at each of the 27 participating centers. All centers except #001 were mailed medication for the randomization of a maximum of 40 patients, with 8 patients in each Tx group (A=8, B=8, C=8, D=8 and E=8). Center #001 was different. Mailed to this center was medication for the randomization of 300 patients, with 60 patients in each Tx group (A=60, B=60, C=60, D=60 and E=60). Two of these five groups corresponded to 20 mg of OME, two to 10 mg of OME and one to PL. In this manner, the randomization scheme (2:2:1) was carried out with the expected number of patients at 200:200:100.

Table 2 shows that the larger number of patients (n=126) was enrolled at Center #1. This was followed by Centers #12 and #22 (40 patients each), Center #10 (24 patients), Centers #9 and #17 (23 patients each) and then Centers #6, 11 and 21 (20 patients each). All the other centers enrolled 19 patients or less. Six centers (#4, 7, 8, 16, 19 and 25) enrolled each 9 patients or less.

The randomization scheme was apparently well-executed. As a result, the number of patients enrolled in the PL, 10 and 20 mg OME groups was 105, 199 and 205, respectively.

TABLE 2

Number of Patients Enrolled Per Center

Center #		PL	OME (mg)		Total
			10	20	
1	Lauritsen/Pederson, Odense ^a	26	50	50	126
2	Lundegardh, Boden	3	5	6	14
3	Carlin, Bollnäs	2	4	5	11
4	Liedberg, Eskilstuna	1	3	3	7
5	Back, Gävle	2	5	4	11
6	Högström, Halmstad	4	8	8	20
7	Oscailsson, Helsingborg	2	1	1	4
8	Sjöstedt, Huddinge	1	2	3	6
9	Forsell, Karlskrona	4	10	9	23
10	Jaup, Göteborg	5	9	10	24
11	Johnsson, Lund	4	8	8	20
12	Anker-Hansen, Motala	8	16	16	40
13		No Patients Recruited			
14	Glise, Trollhättan	4	6	6	16
15		No Patients Recruited			
16	Lundell, Göteborg	1	0	0	1
17	Unge, Sandviken	2	5	5	12
18	Lind, Skövde	5	8	10	23
19	Lindström, Söderhamn	2	4	3	9
20	Everts, Uddevalla	3	5	6	14
21	Martinsson, Varberg	4	8	8	20
22	Stubberöd, Värnamo	8	16	16	40
23	Stenquist, Västra Frölunda	3	8	8	19
24	Thorhallsson, Växjö	4	7	8	19
25	Näslund, Örebro	1	0	2	3
26	Hellblom, Östersund	3	6	6	15
27	Darje, Göteborg	3	5	4	12
	TOTAL	105	199	205	509

a) This center was located in Denmark. All the others were located in Sweden.

• Study Centers #13 and 15 were closed due to lack of patient enrollment.

b. Data Showing Comparability of Treatment Groups at Baseline
(Table 3)

The demographic disease and endoscopic characteristics at baseline are summarized in this Table (APT cohort). A slight imbalance regarding gender and smoking is noted. This imbalance prompted an evaluation of the influence of these two factors on the primary efficacy endpoint. Otherwise the study population was almost exclusively Caucasian, with a 48% of age 18-49y, 37% of 50-64 y and 15% of the patients of age >65 y and 62% alcohol drinkers. Roughly half of the patients had a Hx of duration of symptomatic GERD of 1 to 5y while in the other half the duration of symptomatic GERD was >5y, roughly half of the patients had a hiatal hernia with the majority of patients having normal endoscopic findings in the esophagus, stomach and duodenum. In 33% of the patients the esophageal pH was <4 <4% of the time, in 50% it was >4% of the time; in ca. 11% of the patients, the 24-h intraesophageal acidity measurements were either unknown or invalid. The three test groups were similar to each other regarding all these baseline characteristics.

TABLE 3

Demographic, Disease, Endoscopic and Gastro-Esophageal
 Reflux Characteristics at Randomization

	PL	OND (mg)	
		10	20
TOTAL	105	199	205
SEX			
M	49%	45%	32%
F	51%	55%	68%
RACE			
Caucasian	99%	99%	99%
AGE (y)			
18-49	44%	54%	46%
50-64	39%	35%	36%
>65	17%	11%	18%
Mean (y)	51	49	50
MEAN WEIGHT (Kg)			
M	83	82	79
F	73	70	71
MEAN HEIGHT (cm)			
M	178	178	176
F	164	163	165
SMOKING			
None	63%	58%	65%
Past	16%	12%	12%
Current	21%	30%	22%

ALCOHOL			
None	38%	32%	40%
Past	1%	1%	1%
Current	61%	67%	59%
DURATION OF SYMPTOMATIC GERD			
<1 y	1%	<1%	0%
1-5 y	41%	47%	49%
>5 y	58%	53%	51%
ESOPHAGUS, ABNORMAL FINDINGS			
NO	77%	75%	80%
YES	23%	25%	20%
HIATAL HERNIA			
NO	50%	50%	44%
YES	50%	50%	56%
STOMACH, ABNORMAL FINDINGS			
NO	82%	92%	89%
YES	18%	8%	11%
DUODENUM, ABNORMAL FINDINGS			
NO	93%	97%	96%
YES	7%	3%	4%
PERCENTAGE OF TOTAL TIME WITH pH<4			
<4%	33%	33%	33%
>=4%	56%	55%	56%
Unknown/Invalid	10%	12%	11%

c. Treatment Discontinuations

The number of patients D/C before visit 3 is given below. Among the three test groups, patients were D/C for similar reasons.

Reason for D/C	PL	OME (mg)		Total
		10	20	
RANDOMIZED	105	199	205	509
D/C due to AE	3	2	2	7
Lost to follow-up or unwillingness to continue	0	0	3	3
Persistent/worsening of symptoms	2	1	2	5
Non-compliance with protocol	0	1	1	2
Other	0	0	1	1
Total No. of Pts. D/C	5	4	9	18
Completed Visit 3	100	195	196	491

d. Compliance Data

As shown below, at both periods of evaluation (visit 1-visit 2 and visit 2-visit 3), the bulk of the experimental subjects in each of the three test groups were >90% compliant.

Compliance (%)	PL	OME (mg)		Total
		10	20	
VISIT 1-VISIT 2				
<75%	1	1	5	7
75-90%	4	10	9	23
>90%	97 (92%)	184 (92%)	187 (91%)	468 (92%)
unknown	3	4	4	11
VISIT 2-VISIT 3				
<75%	1	2	4	7
75-90%	8	9	6	23
>90%	90	180	183	453 (89%)
Unknown	6	8	12	26
APT Population. Visit 1 = Baseline Visit 2 = 2 Weeks Visit 3 = 4 Weeks				

e. Protocol Deviations

Shown below is the number of patients by Tx and number of days between visits. Protocol deviations defined in the study protocol prior to breaking the treatment code included intake of <75% of prescribed test med., visits outside the range days, intake of proscribed meds during the trial period, major deviation from inclusion/exclusion criteria and D/C leading to missing efficacy data.

Number of Days	PL	OME (mg)		Total
		10	20	
VISIT 1-VISIT 2				
10	0	4	1	5
11-17	98 (93%)	177 (89%)	189 (92%)	464 (91%)
18	0	7	7	14
>18	5	8	6	19
Visit 2 not performed	2	3	2	7
VISIT 1-VISIT 3				
<21	0	1	0	1
21-22	0	0	1	1
23-33	96 (91%)	182 (91%)	180 (88%)	458 (90%)
34-35	4	8	9	21
>35	0	4	6	10
Visit 3 not performed	5	4	9	18
For the purpose of these evaluations the sponsor considered Protocol Deviations if visit 2 was outside the range 10-18 days and visit 3 outside the range 21-35 days from visit one. The Protocol specified 11-17 days and 23-33 days, respectively, as acceptable ranges.				

f. Disposition of Patients in the Analyses

- This information was presented by the sponsor in their Tables 7, 8 and 9 (vol. 8, p. 55). From these Tables the number of patients by main reason of exclusion is given below.

Main reason for exclusion	PL		OME (mg)				Total	
			10		20			
	v2	v3	v2	v3	v2	v3	v2	v3
Major deviation from incl./excl. criteria	0	0	2	2	1	1	3	3
Discontinued due to AE	1	3	2	2	1	2	4	7
Lost to follow-up or refused to continue	1	1	0	0	1	2	2	3
Non-compl: prohibited concomitant med.	0	0	1	2	2	0	3	2
Non-compl regarding study med.	2	1	2	3	5	4	9	8
Non-compl regarding day of visit	4	0	8	4	5	5	17	9
Other	0	0	0	0	0	2	0	2
All Reasons	8	5	15	13	15	16	38	34

- The number of patients in the analysis summary is as shown below.

	Randomized	APT analysis		PP analysis	
		Visit 2	Visit 3	Visit 2	Visit 3
OME 20 mg	205	205	205	190	189
OME 10 mg	199	199	199	184	186
PL	105	105	105	97	100
TOTAL	509	509	509	471	475

- The reason(s) for exclusion from the analyses for individual patients (sponsor's Table 9) were similar for the three test groups.

g. Efficacy Results

1) Analysis of Primary Efficacy Parameters

a) Complete Relief of HB (Table 4)

For each of the two population analyses (APT = upper panel and PP = lower panel) shown is the proportion of patients experiencing complete relief of HB during the past 7 days after 4 weeks of Tx (visit 3). The PL response was low (APT=13%, PP=14%). Although higher responses were seen with 10 and especially 20 mg, even with the latter, more than half (APT=54%; PP=52%) of the patients had not experienced complete relief of HB after 4 weeks of Tx.

All therapeutic gains displayed in Table 4 were statistically significant. OME doses of 10 and 20 mg were superior to PL, but of the two dose levels of the drug a higher (33%), clinically important therapeutic gain was obtained over PL with the 20 mg dose. Similar results (therapeutic gain of OME 20 mg over PL=34%) were seen in the analysis of the PP population. In addition, both population analyses showed OME 20 mg to be superior to the 10 mg dose level, with a therapeutic gain of 15%.

TABLE 4

**Clinical Response: Analysis of Primary Efficacy Parameter
Complete Relief of HB**

Response by Dose (mg) in %			Therapeutic Gain (%) / p-values		
PL	OME (mg)				
	10	20			
I. APT Analysis (n=509)					
105 14 (13.3%)	199 62 (31.1%)	205 95 (46.3%)	10 vs PL (18%) [0.001] ^a	20 vs PL (33%) [<0.001]	20 vs 10 (15%) [0.002]
II. PP Analysis (n=479)					
100 14 (14%)	186 60 (32.3%)	189 90 (47.6%)	10 vs PL (18%) [0.001] ^b	20 vs PL (34%) [<0.001]	20 vs PL (15%) [0.003]
a,b) The differences between Tx groups were tested using Mantel-Haenszel Chi-square test					

b) Complete Relief of HB by Investigator and Dose

(Data not shown)

- Possible center effects were investigated using the Breslow-Days statistical test. According to the sponsor, there was no indication of inhomogeneity among centers regarding the effects on complete relief of HB [p>0.15 for all three comparisons (OME 10 vs PL), (20 vs PL), (20 vs 10), both in APT and PP analyses].

c) Effects of Gender and Smoking

The impact of gender and smoking, two factors for which some baseline imbalance was found between the Tx groups, was evaluated. A logistic regression model was used with Tx (OME 20 mg/OME 10 mg/PL), gender (M/F) and smoking (YES/NO) as explanatory variables and with complete relief of HB as the dependent variable. For this evaluation, the PP approach was used. This assessment showed little changes in the above-reported treatment effects (see summary display below). These Tx effects were still statistically significant different when gender and smoking were included. With the model, the factors gender and smoking reached p-values of 0.40 and 0.10, respectively.

Proportion (%) of Patients With Complete Relief of HB at the 4-Week Visit by Gender and Smoking Habits

	PL		OME (mg)				Total	
			10		20			
	n	%	n	%	n	%	n	%
GENDER								
M	50	14	82	30	60	57	192	34
F	50	14	104	34	129	43	283	35
SMOKE								
NO	79	15	132	32	150	52	361	37
YES	21	10	54	33	39	31	114	28

For this evaluation the PP approach was used.

2) Analysis of Secondary Efficacy Parametersa) Complete Relief of HB by Percent of Time with pH <4

A logistic regression analysis was used in the PP Population. Factors included only patients given OME (10 or 20 mg), Pre-Tx level of esophageal acid exposure (more/less than 4% of the total time with pH<4) and interaction between Pre-Tx level of esophageal acid exposure and treatment. The dependent variable was complete relief of HB at 4 weeks (visit 3). The results of these analyses are summarized in Table 5. In a model with Tx and acid exposure factors included, Tx gave a statistical significance at p=0.005; acid exposure gave a statistical significance at p=0.009.

TABLE 5

Proportion (%) of Patients With Complete Relief of HB at the 4-Week Visit by Percent of Time with pH<4, Abnormal Esophageal Acid Exposure (4% or more of the total time with pH<4)

	PL		OME (mg)				TOTAL	
			10		20			
	n	%	n	%	n	%	n	%
Total	100	14	186	32	189	48	475	35
% TIME WITH pH<4								
<2	15	7	36	22	32	34	83	24
2-3.99	17	24	26	35	25	36	68	32
4-5.99	16	19	24	33	28	43	68	34
6-9.99	16	19	32	25	34	56	82	37
>=10	25	8	48	46	48	63	121	45
Unknown/Invalid	11	9	20	25	22	41	53	28
Abnormal esophageal acid exposure								
NO	32	16	62	27	57	35	151	28
YES	57	14	104	37	110	55	271	39
Unknown/Invalid	11	9	20	25	22	41	53	28

The reviewer's interpretation of the data in this Table is as follows.

- In the PP population, consisting of 475 patients, 83 (PL=15 + OME 10 mg=36 + OME 20 mg=32) had total time with pH<4 of <2%, 68 patients had a total time with pH<4 of 2 to 3.99%. The addition of these two (83 + 68) gives 151 or 32% of the patients in the trial who did not have abnormal esophageal acid exposure (see lower panel of Table 5).
- 271/475 (or 57%) of the patients did have abnormal esophageal acid exposure. This 271 number arises from the addition of those patients in whom the total time with pH<4 was 4% or higher: 4% to 5.99%=68, 6% to 9.99%=82 and ≥10%=121. Incidentally, similar results were obtained when calculations were done on the basis of the APT population (283/509=56%) of the patients had pathologic GER.
- In 53/475 or 11% of the patients, the results of the test were either unknown or invalid.
- Among the 271 patients with abnormal esophageal acid exposure, the response to OME (complete relief of HB) was:

PL = 14%	OME 10 mg = 37%	OME 20 mg = 55%
Therapeutic Gain Over PL	23%	41%

These percent responses for OME are quantitatively better than those in the entire population (see Table 4) where results were depicted irrespective of the abnormal/normal esophageal acid exposure. But these higher therapeutic gains are due to the fact that the PL response was the same (14%) whereas the response to OME increased.

- Among the 151 patients without abnormal esophageal acid exposure, the response to OME (again, complete relief of HB) was:

PL = 16%	OME 10 mg = 27%	OME 20 mg = 35%
Therapeutic Gain Over PL	11%	19%

which means that even in those patients who did not have pathologic GER, OME 20 mg was more effective than PL.

- Moreover, superiority of OME over PL is also shown among those patients in whom the 24-h intraesophageal acid test was unknown/invalid:

PL = 9%	OME 10 mg = 25%	OME 20 mg = 41%
Therapeutic Gain Over PL	16%	32%

(Note the very low 9% PL response in this group of patients).

- This evaluation is based on the PP approach.
- The difference between the Tx groups were evaluated as in the Clinical Study Report. A Mantel-Haenszel Chi-square test was used with the significance level adjusted for the three Tx comparisons according to the Bonferroni inequality. In this NDA addendum, stratification on center was not done to avoid strata with zeros in the rows or columns. Confidence intervals (95%) were completed using the normal approximation. Effects of age, gender and evaluating center were also assessed.

b) Severity and Frequency of HB (Table 6)

There is not much that can be said of the quantitative differences between the treatments being compared in this Table. All three treatments are switching the severity of HB toward less severe categories. As already pointed out (Table 4) the OME 20 mg dose was more effective than PL and the OME 10 mg dose in the proportion of patients in the NONE category of severity. Ca. half of the patients with MOD HB at BL had MOD HB at visit 2 and there was no change at week 3. With OME, the number of patients with MOD HB at BL that had MOD HB at visit 2 had decreased to <1/3 with some further improvement at visit 3. The proportion of patients with severe HB at BL was higher in the PL group (16% of the pts) than in the OME groups (12% and 13% of the patients). This was a consequence of the randomization process, but at least in this category (severe HB) the BL values were quantitatively biased against PL. But by visit 2 and visit 3, the proportion of patients with SEV HB in the OME groups (2% to 4%) were lower than those in the PL-treated group (8% to 9%).

TABLE 6

Number of Patients (%) by Severity of HB and Frequency of Episodes of HB During the Last 7 Days, at Each Visit

	PL			OME (mg)					
				10			20		
	v 1	v 2	v 3	v 1	v 2	v 3	v 1	v 2	v 3
Total n =	105	97	100	199	184	186	205	190	189
SEVERITY									
NONE	0	9 (9%)	14 (14%)	0	52 (28%)	60 (32%)	0	73 (38%)	90 (48%)
MILD	45 (43%)	57 (59%)	53 (53%)	64 (32%)	91 (49%)	93 (50%)	77 (37%)	76 (40%)	65 (34%)
MOD	43 (41%)	22 (23%)	23 (23%)	112 (56%)	35 (19%)	28 (15%)	102 (50%)	34 (18%)	26 (14%)
SEV	17 (6%)	8 (8%)	9 (9%)	23 (12%)	6 (3%)	4 (2%)	26 (13%)	7 (4%)	5 (3%)
Discontinued Tx Fx	0	0	1 (1%)	0	0	1 (<1%)	0	0	3 (2%)
Unknown	0	1 (1%)	0	0	0	0	0	0	0
FREQUENCY (days)									
NONE	0	9 (9%)	14 (14%)	0	52 (28%)	60 (32%)	0	73 (38%)	90 (48%)
1	0	12 (12%)	11 (11%)	0	26 (14%)	34 (18%)	0	25 (13%)	28 (15%)
2-4	52 (50%)	26 (27%)	29 (29%)	87 (44%)	49 (27%)	35 (19%)	89 (43%)	38 (20%)	26 (14%)
5-6	18 (17%)	18 (19%)	15 (15%)	24 (12%)	26 (14%)	27 (15%)	26 (13%)	19 (10%)	13 (7%)
7	35 (33%)	32 (33%)	30 (30%)	88 (44%)	31 (17%)	29 (16%)	90 (44%)	35 (18%)	29 (15%)
Discontinued Tx Fx	0	0	1 (1%)	0	0	1 (<1%)	0	0	3 (2%)

Similar quantitative effects were seen when comparing the frequency of HB (days) as a function of Tx (PL vs OME). For example, the OME 20 mg dose (38% to 48%) was more effective than PL (9% and 14%) and the OME 10 mg dose (28% and 32%) in the proportion of pts. in the NONE category of frequency. Thirty-

three percent of the PL-treated pts. had HB with a frequency of 7 days at BL. This proportion decreased very little (to 33% at visit 2 and 30% at visit 3). On the other hand, with OME the proportion of patients experiencing HB with a frequency of 7 days at BL (10 mg=44%; 20 mg=44% pts.) decreased to 17% and 18% by visit 2, 16% and 15%, in the OME 10 and 20 mg, respectively, at visit 3.

c) Other Symptoms

Compared below are the proportion (%) of patients with no symptoms as a function of symptom, Tx and visit, overall symptoms now and specific symptoms during the last 7 days. For the categories overall and heartburn, both OME groups gave higher percentages of patients with no symptoms in comparison to PL. But the differences for the other symptoms are not very marked among the Tx groups.

	PL			OME (mg)					
				10			20		
	v 1	v 2	v 3	v 1	v 2	v 3	v 1	v 2	v 3
OVERALL	5	11	18	3	30	33	4	35	42
HEARTBURN	0	9	14	0	28	32	0	38	48
REGURG.	35	48	47	31	55	58	36	56	65
DYSPHAGIA	79	85	83	83	89	91	69	83	90
EPIG. PAIN	40	54	62	39	60	68	41	62	72
NAUSEA	64	72	78	62	77	77	64	77	79
VOMITING	91	95	94	92	95	97	94	95	95

For these evaluations the PP approach was used.

h. Results of Safety Evaluations

- In this study, the total number of patients exposed were:

PL = 105 OME 10 mg = 199 OME 20 mg = 205

- There were no noticeable differences among the three test groups in the number of patients experiencing serious AEs and those in whom the test med. had to be completely or temporarily stopped due to AE.
- Of the 4 patients experiencing SAEs during the trial (OME 10 mg, n=2; OME 20 mg, n=2), arthralgia and enterocolitis occurring in Pt. No. 0010073 (M, aged 23), who was randomized to OME 10 mg, were considered possibly related to the drug; the other three were considered unlikely related to test med. However, Giardia lamblia, found in the feces and treated with metronidazole, was the more likely cause of the enterocolitis in Pt. 0010073.
- The number of patients in whom drug was stopped due to AE was similar among the test groups (PL, n=5; OME 10 mg, n=4; OME 20 mg, n=3). Except

for the aforementioned case of enterocolitis (Pt. 0010073), which was considered serious, all of these cases were non-serious. A case by case review of these cases revealed that they were unlikely related to test med.

- Irrespective of Tx, 198 of the 509 patients reported a total of 323 AEs. The total number of patients experiencing AEs per group was:

<u>PL</u>	<u>OME 10 mg</u>	<u>OME 20 mg</u>
n=105	n=119	n=205
46/27	98/70	117/72

- In their Appendix 3, the sponsor presented a summary of patients with AEs by system organ class for all AEs and for new-onset AEs, respectively. AEs ordered by frequency were also given in sponsor's Appendix 3.
- Patients are listed by the most common AEs in Table 7. Only AEs occurring for >2 patients are included. The AEs are listed in order of frequency in the double-blind study. Emphasis is placed on the incidence of AEs with the 20 mg OME in comparison to the 10 mg OME. The type and frequency of AEs reported for the two OME regimens and PL were essentially similar. The most commonly reported AEs were symptoms from the g.i. tract (i.e. diarrhea), headache and respiratory infection (i.e. common cold, the most frequently reported AE within the respiratory system organ class).

TABLE 7

Number (%) of Patients by the Most Common AEs

	PL n=105	OME (mg)	
		10 n=199	20 n=205
Diarrhea	4 (3.8)	12 (6.0)	10 (4.9)
Headache	3 (2.9)	9 (4.5)	12 (5.9)
Respiratory infection	1 (1.0)	12 (6.0)	7 (3.4)
Flatulence	0	6 (3.0)	6 (2.9)
Constipation	1 (1.0)	6 (3.0)	4 (2.0)
Nausea	2 (1.9)	3 (1.5)	7 (3.4)
Abdominal pain	3 (2.9)	3 (1.5)	3 (1.5)
Gastroenteritis	1 (1.0)	4 (2.0)	1 (0.5)
Dizziness/vertigo	3 (2.9)	2 (1.0)	3 (1.5)

Pharyngitis	1 (1.0)	1 (0.5)	2 (1.0)
Fatigue	2 (1.9)	1 (0.5)	2 (1.0)
Infection viral	1 (1.0)	3 (1.5)	2 (1.0)
Back pain	0	2 (1.0)	4 (2.0)
Vomiting	0	3 (1.5)	3 (1.5)
Bronchitis	0	3 (1.5)	1 (0.5)
Arthralgia	1 (1.0)	2 (1.0)	0
Coughing	0	2 (1.0)	1 (0.5)
Insomnia	1 (1.0)	1 (0.5)	2 (1.0)
Myalgia	1 (1.0)	1 (0.5)	1 (0.5)
Pain	0	1 (0.5)	0
Pharynx disorder	0	1 (0.5)	1 (0.5)
Rhinitis	0	2 (1.0)	2 (1.0)
Sinusitis	1 (1.0)	1 (0.5)	1 (0.5)
Tooth disorder	0	2 (1.0)	1 (0.5)
Accident and/or injury	0	2 (1.0)	1 (0.5)
Allergic reaction	0	1 (0.5)	1 (0.5)
Conjunctivitis	0	2 (1.0)	1 (0.5)
Cystitis	0	1 (0.5)	0
Dyspepsia	0	0	1 (0.5)
Epigastric pain	0	0	2 (1.0)
Pruritus	0	0	3 (1.5)
Rash	1 (1.0)	2 (1.0)	0
Taste perversion	0	1 (0.5)	1 (0.5)
Tongue disorder	2 (1.9)	0	1 (0.5)
Weight increase	1 (1.0)	1 (0.5)	1 (0.5)
The AEs are classified in accordance with the preferred term level, i.e. AEs of a similar kind share the same preferred term.			

8. Conclusions (Sponsor)

"This study shows that both omeprazole 20 mg o.m. and 10 mg o.m. are superior to placebo in providing effective and rapid relief of heartburn in patients with symptoms of reflux disease but without endoscopic evidence of esophagitis. Omeprazole 20 mg is more effective than omeprazole 10 mg.

"The probability of success (i.e. complete relief of heartburn) was greater in patients with higher pre-treatment levels of acid gastroesophageal reflux in the omeprazole-treated groups than in those with low or normal acid reflux.

"Both omeprazole 20 mg and 10 mg are superior to placebo in improving patient's general well-being. A similar pattern in favour of omeprazole was seen for relief of reflux symptoms as assessed by the GSRS (Gastrointestinal Subjective Rating Scale).

"Omeprazole was in general well-tolerated."

9. Comments (Reviewer)

The sponsor submitted results of non-US study I-1601a for the approval of PRILOSEC® (OME) for the treatment of symptomatic GERD. The eventual implication is that OME, 20 mg once a day, is indicated for the treatment of heartburn and other symptoms associated with GERD in both patient populations: those with erosive esophagitis and those with endoscopically negative disease. This supplemental application is concerned only with the latter type of patient (non-erosive esophagitis). Data on the treatment of symptoms associated with erosive esophagitis was reviewed in the original NDA 19-810 submitted in 1988.

Study I-1601a was designed to test the efficacy and safety of two dose levels of OME, 10 and 20 mg once-a-day, in comparison to once-a-day PL, a negative control, on the relief of GERD symptoms over a period of 4 weeks. The main symptom assessed, heartburn, is believed to be typical of GERD, but the relief of other symptoms, such as regurgitation et al., was also assessed. In addition to using an appropriate control, an interesting feature of this trial was the performance of L-T (24-h) intraesophageal pH monitoring.

There is presently no absolute "gold standard" test for GERD, but it is now widely accepted that 24-h esophageal pH-monitoring is the best available diagnostic test. According to a report by H.E. Mattox and J. Richter [Amer. J. Med. 82:345-356 (1990)], the sensitivity and specificity of pH-monitoring ranges between 90% and 100% in patients with reflux esophagitis. But, according to J-P Galmiche et al. [Scand. J. Gastroenterol. 22(Supl. 201):63-68 (1994)] the sensitivity of pH-monitoring is probably lower in patients with less severe disease (see below).

In spite of some unresolved uncertainties, the reviewer believes that the use of this diagnostic procedure is very important because it objectively documents the presence of pathological GER. This evaluation demonstrates that reflux indeed exists and to what degree. This tool may also be useful to demonstrate whether reflux was responsible for the patient's symptoms (see below).

Another interesting feature of this trial was that all patients were endoscoped pre-randomization. This procedure identified a group of patients who had symptoms believed to be typical of GERD (heartburn, regurgitation) but

who had no esophageal lesions thought to be the result of reflux damage to the mucosa. The protocol stipulated that only the former group of patients were to be randomized. Patients with esophageal lesions were not to be randomized. In spite of these plans, according to the clinical report, 115 of the 509 (or 23%) patients did have pre-entry abnormal endoscopic findings. This information was submitted by the sponsor on April 5, 1996, in response to a request for clarification on this matter from the Medical Officer (handled through the CSO). These data, summarized below, are included here to document that these pre-entry abnormal endoscopic findings would not have a significant impact on outcome. The endoscopic findings cannot be categorized as representing "esophagitis". For practical purposes, the patients randomized in Study I-1601a had primarily symptomatic GERD. Nonetheless, since suction biopsy of the esophageal mucosa was not done, it is not known whether the randomized patients had histological changes due to reflux. The nature of the clinical condition being treated was such that the patients enrolled in this trial did not use any lifestyle modifications (elevation of the head of the bed, not eating for 2 to 4h prior to going to bed or reclining at the sofa, or dietary modifications).

Study I-1601a

Preentry Abnormal Endoscopic Findings

	PL (n=105)	OME (mg)	
		10 (n=199)	20 (n=205)
No. of Patients (%)			
<u>Abnormal Findings</u>			
Erythema	17 (16%)	32 (16%)	28 (14%)
Erythema & Friability	1 (<1%)	1 (<1%)	1 (<1%)
Grade 1 Esophagitis	5 (5%)	13 (7%)	11 (5%)
Edema, Irregular Z-line	0 --	0 --	1 (<1%)
Redness in Distal Esophagus	1 (1%)	2 (1%)	1 (<1%)
Non-erosive	0 --	1 (<1%)	0 --
Total Patients	24 (23%)	49 (25%)	42 (20%)
<p>NOTE: These data are presented for completeness. In their submission of April 10, 1996 the sponsor clarified that Grade I esophagitis, according to a modification of the Savary Miller gradings corresponded to No Macroscopic erosions visible. Erythema or diffused red mucosa; edema causing accentuated folds. Therefore, patients in study I-1601a had symptomatic GERD, with neither erosions nor ulcerations of the esophageal mucosa (endoscopically negative GERD).</p>			

This multicenter, parallel group, 3-arm study used an adequate randomization scheme and was double-blind in design. The inclusion-exclusion criteria were

adequate in that patients with potentially confounding conditions or diseases or taking potentially confounding medications were excluded. But all patients were allowed to take antacids during the trial. A total of 509 patients were enrolled by 25 centers, in a 1:2:2 proportion (PL=105, OME 10 mg=199, OME 20 mg=205). The largest number of patients (n=126 or 25% of the total) were enrolled in Center #1 Denmark. The test group response in this center is mentioned below.

The randomization process resulted in three Tx groups that were similar to each other in their demographic characteristics, smoking habits, history of alcohol intake and duration of symptomatic GERD, as there were no statistically significant differences in any of these characteristics among the three Tx groups. Similarly, the three Tx groups were balanced in regard to presence/absence of hiatal hernia, endoscopic findings in the duodenum and the stomach (most patients did not have abnormal endoscopic findings in these organs) and the above-referred abnormal endoscopic findings in the esophagus. The Tx groups were also balanced with respect to a) the proportion of patients with <4% (33% per group) total time with pH<4 in the esophagus and b) the proportion of patients with ≥4% total time with pH<4 in the esophagus (56%, 55% and 56% for the PL, 10 and 20 mg OME groups, respectively). The three groups of patients were also well-balanced in treatment discontinuations, compliance with test medication, protocol deviations and the main reason for exclusion from the PP analyses. Because of these similarities, PP analyses very closely reproduced the APT analyses. Consequently, only the latter are mentioned in the conclusions drawn below. Also, for simplification purposes, the reviewer's comments refer to results of analyses of a) the primary efficacy parameter prospectively identified in the protocol, namely, proportion of patients with complete relief of heartburn and b) the main secondary parameter of efficacy, assessment of the pre-treatment level of esophageal acid exposure as prognostic factor.

Results of this study, on the primary efficacy parameters, complete relief of HB at the 4-weeks visit, supported superiority of each of the two dose levels (10 and 20 mg) of OME over PL and of the 20 over the 10 mg of OME. The response to PL (13%) was considerably lower than the expected response on the basis of sample size determination (40%). Also, considerably lower than expected were the responses with 10 (31% observed; 70% expected) and the 20 mg dose of OME (46% observed; expected=85%). In summary, these data showed a therapeutic gain of 18% for OME 10 mg vs PL and 33% for OME 20 mg vs PL. These are appropriate for regulatory purposes since with this information one can answer the first two questions regarding the Tx of Symptomatic GERD.

Q. Do the study results demonstrate efficacy?

- A. Yes.** Efficacy was shown for both levels of OME. The therapeutic gains over PL were 18% for the 10 mg and 33% for the 20 mg dose. Both differences (over PL) were statistically significant (p=0.001).

Q. Can a treatment dose (10 vs 20 mg) be identified and recommended?

A. With the information at hand, the answer to this question is not so simple. Based on therapeutic gains over PL, one would have to choose 20 over 10 mg of the drug. This is because there are no safety concerns for the S-T use of either 10 or 20 mg OME in this patient population [The answer to Question 3. is NO]. But if one chooses 10 mg, 69% of the patients would not experience complete HB relief and this is clinically unacceptable. Moreover, when choosing 20 mg, one is identifying a dose of the drug that is identical to the recommended dose for healing of erosive esophagitis and this is contrary to what most experts in this field propose to treat symptomatic GERD with no esophageal lesions vs the symptoms of GERD in patients that have erosive esophagitis. The latter supposedly and practically requires higher total daily doses or more frequent administration of low doses of antisecretory drugs than the former. But, more importantly, how can one recommend a dose of the drug that although effective, gives disappointing results since, even with 20 mg once-a-day OME, 54% (more than half) of the patients would not experience complete heartburn relief?

Can explanations for these disappointing findings be found in the results of analyses of complete relief of HB by percent of time with pH<4?

The 24-h esophageal pH monitoring is based on a sound general principle. Good evidence is now available that once the intra-esophageal pH rises above 4, the luminal environment of the esophagus is relatively non-injurious to the esophageal squamous mucosa. This evidence originates both from animal models of reflux disease [H.I. Goldberg et al., *Gastroenterology*, 56:223-230 (1969); R.C. Orlando et al., *Amer. J. Physiol.* 246:G718-724 (1984); and J.L. Goldstein et al., *Gastroenterol. Clin. North Amer.* 19:565-586 (1990)] as well as pH-monitoring studies of the therapy of reflux disease with acid inhibition [E.C. Klinkenberg-Knol and S.G. M. Meuwissen, *Digestion*, 51(Suppl. 1):44-48 (1992); M. Ruth et al., *Scand. J. Gastroenterol.* 23:1141-1146 (1988)].

The definition of pathologic GER (abnormal esophageal acid exposure) in this study was as in many reports in the literature: pH<4 in the distal esophagus for 4% or more of the pH-monitoring time [for a review of this matter see J. Dent, *Scand. J. Gastroenterol.* 29(Suppl.201):55-61 (1994)]. A total of 271/475 or 57% in the PP population (283/509 or 56% in the APT population) had pathologic GER in study I-1601a, 151/475 or 32% of the patients did not have abnormal esophageal acid exposure and in 53/475 or 11% of the patients, the results of the test were either unknown or invalid. In spite of these findings, for the primary efficacy parameter (complete relief of HB), effectiveness (OME better than PL) was shown in the three groups of patients. Since the results of most interest are those from patients with abnormal esophageal acid exposure, these data are summarized below (APT analyses):

	<u>PL</u>	<u>10</u>	<u>20</u>
Complete Response	14%	36%	56%
Therapeutic Gain (over PL)/p-value		22% [p<0.003]	42% [p<0.001]
Therapeutic Gain (over 10 mg)/p-value			20% [p=0.003]

PP Analyses resulted in similar results

The above-summarized results are good for regulatory purposes in that both dose levels of OME are effective (superior to PL) and the 20 mg is superior to the 10 mg dose. All of this has been shown in the study population where an effect is needed, because the patients have pathologic GER. Once again, the results are disappointing because if one chooses 10 mg of the drug, complete relief of HB would not be achieved in ca. 2/3 (64%) of the patients. Even if one were to choose 20 mg, with this dose level of the drug, 44% of the patients would not experience complete relief of HB.

As already mentioned, in addition to the group of patients shown to have pathologic GER, there were two additional groups. The efficacy results in the other two groups of patients are intriguing. Although the response with OME 20 mg was only 35% among those patients who did not have an abnormal esophageal exposure on the basis of the 24-h test, this represented a clinically important therapeutic gain of 19% over PL. These results are not easily understood. While searching for a plausible explanation, it is important to reiterate that, as pointed out in the Introduction section of this review, OME appears to have no other pharmacological properties than antisecretory. The results in the group of patients with unknown/invalid 24-h pH test results were equally intriguing: these were not dissimilar from those observed in the general population.

The preceding discussion attributes a high level of sensitivity and specificity to the 24-h esophageal pH-monitoring test. But in reality, the accuracy of this diagnostic test, in patients who do not have esophageal lesions like those that are the subject of the present study, is largely unknown. The accuracy characteristics of the test as reported by Mattox and Richter [locus cited (1990)], of ranges between 90% and 100% for sensitivity and specificity, were derived from evaluations in patients that had endoscopically proven esophageal lesions. Even in these patients, the relationship between symptoms and acid exposure is controversial. A report by Joelsson and Johnsson [Gut, 30:1523-11525 (1989)] showed that there was a definite relationship between the degree of acid exposure and the frequency of HB: the greater the acid exposure, the more frequent the symptoms. This relationship is graphically documented in the Fig. 1, taken from the publication by Joelsson and Johnsson:

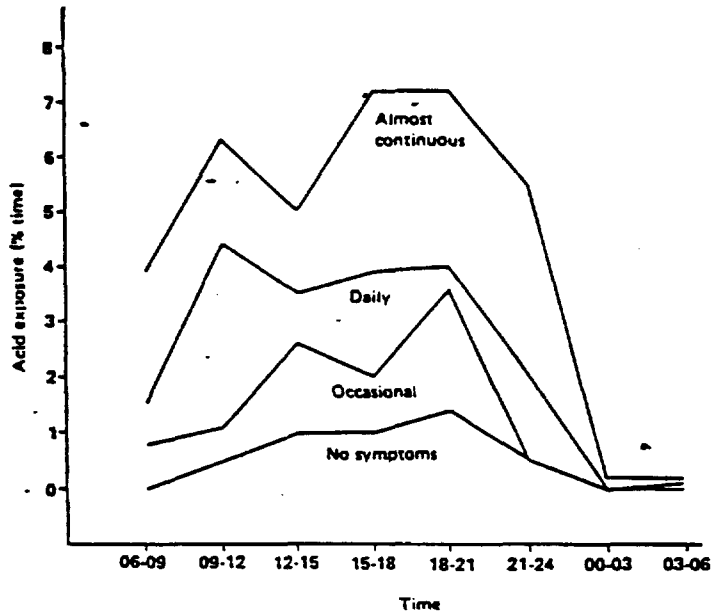


Fig. 1: Acid exposure of the distal part of the esophagus during eight three hour periods expressed as median % time spent with pH<4 in 190 patients with different degrees of heartburn and acid regurgitation and 50 asymptomatic endoscopically normal subjects.

According to these authors this relationship was observed in patients either with or without esophagitis. These authors also noted that patients with almost continuous symptoms had maximal acid exposure in the late afternoon and evening. But these interesting observations have not been replicated. On the contrary, the study of M. Atkinson and A. Van Gelder [Dig. Dis. Sci., 22:365-370 (1977)] failed to establish such a close correlation between the HB score and the duration of acid exposure. Although most acid reflux episodes are not accompanied by reflux symptoms [F. Baldi et al., Dig. Dis. Sci. 34:1890-1893 (1989)], some patients experience severe symptoms of HB, which are highly correlated with short-lived reflux episodes in the absence of abnormal 24-h esophageal acid exposure [S. Bruley des Varannes et al., Gastroenterology 102:A45 (1992)]. Here, it is important to mention the work of J. Janssens et al. [Gastroenterology 102:A90 (1992)] who showed that the level of acid exposure during the period preceding a particular reflux episode is a major determinant of whether that reflux episode will result in symptoms. These authors termed this acid exposure the "acid burden", which expresses the previous priming of the esophageal mucosa by acid, thereby making the mucosa more sensitive to a subsequent acid reflux episode. It is also of interest to mention studies measuring pH in both the upper and lower esophagus, such as those reported by P. Jacob et al. [Gastroenterology, 100:305-310 (1991)] and P.O. Katz [Amer. J. Gastroenterol. 85:38-40 (1990)]. Results of the latter studies indicated that patients with throat symptoms (e.g. chronic hoarseness, with or without signs of posterior laryngitis) may have more prolonged acidification of the proximal esophagus, particularly during the night,

suggesting that these symptoms may result from acid spill into the larynx. But in reality, the origin of symptoms and the mechanisms whereby they arise during reflux are not fully understood.

There is more information on the relationship between symptoms and lesions of esophagitis. As indicated in a recent review by J.P. Galmiche and S. Bruley des Varannes [Scand. J. Gastroenterol. 22(Suppl.201):62-68 (1994)] symptoms cannot be used to predict reliably the presence and severity of esophagitis. Indeed, at least 50% of patients with symptoms suggestive of GERD have no mucosal lesions visible on endoscopy [F. Johnsson et al., Scand. J. Gastroenterol. 22:714-718 (1987); P. Zeitoun and E. Carteret, Natural history of reflux esophagitis in adults. In: Mignon M. Galmiche J-P, editors. Control of acid secretion. Paris, London: J Libbey:225-238 (1988)]. Also, HB may be absent in patients with severe reflux esophagitis and ca. 25% of patients with Barrett's mucosa have no symptoms of esophageal disease [S.J. Spechler, Digestion, 51Suppl 1:24-29 (1992)]. A.J. Cameron and his co-workers [Gastroenterology 92:918-922 (1990)] believe that perhaps this explains, at least in part, why many cases of Barrett's esophagus identified on autopsy remain unrecognized during life. Similarly, in a large number of patients with peptic stricture, only one-third had a previous Hx of reflux symptoms [M. Ben Rejeb, Dig. Dis. Sci. 37:733-736 (1992)]. However, when HB occurs in association with peptic stricture, there is usually a longer Hx of reflux symptoms than occurs in patients with Hx but without stricture [G. Atharidis et al., Dig. Dis. Sci. 24:858-861 (1979)].

In conclusion, on the basis of the pertinent published information reviewed above, no plausible explanation can be advanced for a) the disappointing efficacy of OME, even at the daily dose of 20 mg, on the complete relief of HB in study I-1601a, either in the general population or in those patients that were shown to have abnormal esophageal acid exposure and b) the effectiveness of the drug (admittedly low but statistically and clinically significant in comparison to PL) in those patients that were shown not to have abnormal esophageal acid exposure. There is no explanation for the lower response rates even for PL-treated patients (40% projected, 13% to 14% found) but especially for those patients treated with 20 mg of the drug (85% projected, 46% to 48% found). In the APT population, the proposed difference (therapeutic gain) between OME 20 mg and PL fell short by 12% (45% proposed, 33% found). These results are particularly difficult to understand because the majority of the patients randomized in Study I-1601a had moderate to mild symptoms of HB and only a relatively small proportion (16%, 12% and 13% in the PL, 10 mg and 20 mg OME groups, respectively) had severe HB.

The reviewer found it of interest to compare the performance of OME in the present trial in symptomatic GERD vs the effects on the symptoms in those patients who had esophagitis (original NDA 19-810). Unfortunately a 10 mg dose of OME was not included in the clinical trials, reviewed in support of the erosive esophagitis indication. But there was ample demonstration for the effectiveness of 20 mg of the drug. The material that follows was taken from MOR of NDA 19-810, dated March 10, 1989. There were six double-blind controlled studies conducted by Häessle overseas in patients with

endoscopically proven GERD randomized to a) OME 20/40 mg vs PL (Study I-609A), b) OME 20 mg vs 40 mg (Study I-609B), c) OME 20 mg vs RAN 150 mg b.i.d. (Study I-608 and I-619), d) OME 40 mg vs RAN 150 mg b.i.d. (Study I-603) or e) OME 60 mg vs RAN 150 mg b.i.d. (Study I-602). These studies showed clear-cut superiority of OME 20 mg to PL and to 150 mg b.i.d. RAN (an inadequate dose for comparison since the recommended dose for healing is 150 mg q.i.d.) and no special advantage when increasing the dose to higher than 20 mg once-a-day. Results of these trials also showed effectiveness in the relief of HB with OME (82% of the patients) which was shown to be superior to both PL (12%) and to RAN 150 mg b.i.d. (52%). Total relief of HB at the end of the 4 to 8 week trial in those patients with HB at BL was 84% with 20 mg OME. Again, there was no significant further improvement when increasing the dose of OME to doses higher than 20 mg (i.e. 40 or even 60 mg once-a-day). As indicated on page 416 of MOR of NDA 19-810 (March 10, 1989), these evaluations demonstrated that the 20 mg was optimal not only in terms of total healing rates, but also in terms of total relief of HB. Moreover, symptomatic relief with OME seemed to occur earlier (by two weeks) than that seen with RAN 150 mg b.i.d. (page 204 of MOR of March 10, 1989).

The 12% symptomatic response to PL in the above-mentioned European trials in erosive esophagitis patients is very similar to the 13% found in Study I-1601a (also European=Scandinavia) in patients with symptomatic GERD without esophageal lesions. But the response to 20 mg OME is very different (84% vs 46%). The reviewer's obvious conclusion with the information at hand is that for symptomatic GERD, the 20 mg OME once-a-day is effective but not optimal. That there is plenty room for improvement and that this single dose of OME may actually disadvantage patients. One intriguing question is whether better symptomatic response can be achieved with divided doses of the drug, such as 10 or even 5 mg b.i.d. Although the pathophysiology of symptomatic GERD is such that more than once-a-day dosage with an antisecretory drug may be needed to achieve optimal results, there are simply no data in support of these assumptions.

The reviewer requested of the sponsor any data, unpublished or in the literature where the effects of OME, at the oral dose of 10 or 20 mg, have been evaluated in patients with symptomatic GERD without endoscopically detectable esophagitis. In answer to our request, Astra Merck conducted literature searches of commercial databases. They also searched for their own regulatory files, and asked their parent company, Astra to do the same. They were able to locate one additional report: Astra study I-684 entitled: "Heartburn: A randomized placebo controlled study of the effects of treatment with omeprazole 20 mg o.m. on symptoms and patients' lifestyle (HARMONY)". They included a copy of the clinical study report for I-684 in their submission of April 10, 1996. An initial assessment of the results of this study showed that, by four weeks of Tx, more patients in the OME group were heartburn free after 4 weeks of Tx than in the PL group (HB free, 50/87=57% vs 18/95=19%; $p < 0.0001$). With a therapeutic gain of 38%, this study indeed, as the sponsor states, support the findings of I-1601a (NDA supplement reviewed here). There is no question that OME 20 mg once-a-day is more effective than PL for symptomatic GERD. But there is also no question that the performance

of this dose and dose regimen of this PPI in symptomatic GERD is disappointing. In letter dated April 25, 1996 from the Division Director, HFD-180 to sponsor, mention is made that in Study I-1601, which involved symptomatic GERD patients without erosive esophagitis, complete relief of heartburn occurred in 46% of patients taking omeprazole 20 mg qd versus 13% of patients taking PL. We also noted that the average efficacy result in the six GERD studies submitted in the original NDA, which involved symptomatic GERD patients with erosive esophagitis, was 84% (20 mg group) versus 12% (placebo group). The sponsor was asked to consider these findings and to provide their view as to why the percentage of patients experiencing complete relief of heartburn is much lower in Study I-1601 (46%) as compared to the average result of the six original studies (84%), especially in light of very similar results in the placebo groups (13% and 12%, respectively).

[Reviewer's Note: Although the sponsor's response to the above inquiry is of interest, such information would not seem needed to finalize the Medical Officer's review of NDA 19-810/Supplement S-036.]

III. RECOMMENDATIONS FOR REGULATORY ACTION

1. For the treatment of symptomatic GERD in patients with no endoscopic lesions, the omeprazole 20 mg once-a-day dose is approvable.

At a level of only 31%, the response rate with the omeprazole 10 mg daily dose, although superior to placebo (therapeutic gain 18%), cannot be recommended because with this dose 69% of the patients would not experience complete relief of heartburn. Based on the review of the evidence in NDA 19-810/S-036, the reviewer recommends 20 mg with reservations. These reservations are due to the fact that, although with this dose, the 33% therapeutic gain over placebo was both clinically and statistically significant, the rate of complete relief of heartburn was a disappointing 46%. These disappointing results were replicated in another study in symptomatic GERD. Although in the real world the response could be better or worse, the fact that this low response was replicated appears to suggest that roughly half of the symptomatic GERD population would not be optimally treated at a dose level of 20 mg. Both the prescribing physician and the patient must be informed of the low response rate with omeprazole 20 mg once-a-day in Study I-1601a and this can be done by presenting the clinical data in the labeling (see below).

2. The following labeling revisions under CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION are recommended. The reviewer recommendations are listed side-by-side to the sponsor's proposals.

I. Under CLINICAL PHARMACOLOGY . . .

Gastroesophageal Reflux Disease (GERD)

Sponsor's Proposal	MO Recommendations
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II. Under INDICATIONS and USAGE

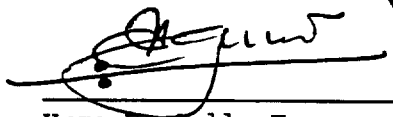
Sponsor's Proposed	MO Recommendations
<p>Treatment of Gastroesophageal Reflux Disease (GERD)</p>	<p>Change is Acceptable</p>
<p><i>Erosive Esophagitis</i> PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy (see CLINICAL PHARMACOLOGY, Clinical Studies). (see CLINICAL PHARMACOLOGY, Clinical Studies.)</p>	<p>Change is acceptable</p>
<p>Delete all references to Poorly Responsive Symptomatic GERD</p>	<p>Change is acceptable</p>

III. Under DOSAGE AND ADMINISTRATION

Sponsor's Proposal	MO Recommendations
<p><u>Delete:</u></p> <p><u>Add:</u></p>	<p>Deletion is acceptable</p>

3. The data in NDA 19-810/S-036 showed that with 20 mg omeprazole once-a-day, more than half of the symptomatic GERD population would not be optimally treated, a finding that was replicated in another symptomatic GERD trial. These clinical data are of concern to the Medical Officer. The approval of this relatively high dose of omeprazole for this indication should be conditioned to the sponsor agreeing to conduct studies aimed at improving the disappointing performance of the drug in this patient population. The Medical Officer recommends to test the effects of low doses of omeprazole given in divided doses (i.e. 5mg b.i.d. vs 10 mg b.i.d. vs 20 mg b.i.d. in comparison to b.i.d. placebo) in patients with heartburn symptoms without endoscopically proven esophageal lesions.

June 13, 1996



Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
 NDA 19-810
 HFD-180
 HFD-180/SFredd
 HFD-180/HGallo-Torres
 HFD-181/CSO
 HFD-180/JChoudary
 HFD-180/EDuffy
 r/d 5/7/96 jgw
 f/t 6/12/96 jgw
 MED\I\19810605.OHG

6/12/96
 JP

STATISTICAL REVIEW & EVALUATION

Date: NOV 25 1996

NDA: 19-810, S-036

Pharmacologic Category of the Drug: proton pump inhibitor

Name of Drug: Prilosec/Losec® (Omeprazole)

Date Received in Division: 1mo//1996; assigned 1mo/11/1996

Date of 45 Day Meeting: 1mo/31/1996

Sponsor: Astra Merck

Indication: short-term first line treatment of GERD

Documents Surveyed: Vols 1,3-7 of 9, dated 12mo/27/1995; supplements dated 8/29/1996 and 10/24/1996

This submission and review have been discussed in general with the medical officer, Dr. Gallo-Torres, M.D., Ph.D.

I. INTRODUCTION

The sponsor wishes to make (editorial) changes with respect to *erosive* versus *symptomatic* esophagitis, and focus on the 20mg dose.

The sponsor wants to change the claim to "first-line" therapy, from (V100.1, pg 2-00009), with bold added for emphasis by this reviewer:

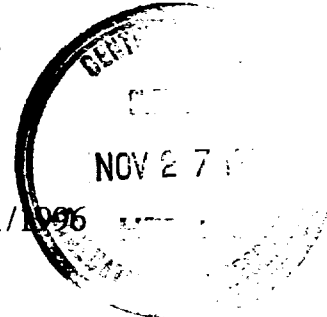
Poorly Responsive Symptomatic GERD

PRILOSEC Delayed Release Capsules are also indicated for the short-term treatment (4-8 weeks) of symptomatic gastroesophageal reflux disease (esophagitis) **poorly responsive** to customary medical treatment, ...

The sponsor wants to replace this with:

Symptomatic GERD

PRILOSEC Delayed-Release Capsules are indicated for the treatment of



heartburn and other symptoms associated with GERD.

The sponsor wishes to change the labeling to include summary results of the Scandinavian study (I-1601a), adding (V100.1, pg 2-00006):

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Significantly more patients taking 20 mg omeprazole reported complete resolution of heartburn symptoms than patients receiving either 10 mg omeprazole or placebo.

II. DESCRIPTION OF TRIAL AND SPONSOR'S ANALYSES AND RESULTS

The study objectives were to show efficacy, evaluate the pre-treatment level of esophageal acid exposure as a prognostic factor for the relief of heartburn, and evaluate Quality of Life changes with regard to general well-being and upper gastrointestinal subjective symptoms from baseline to four weeks.

a) Description of Astra Hässle AB's Trial I-1601a, Scandinavia

i) This blinded three arm study had 27 centers, with patients treated in 25. The number of patients treated was 205 20mg, 199 10mg, and 105 placebo. The randomization was 2:2:1. Within each center, the randomization was in blocks of size 5 patients, with the block size not to be disclosed to the investigators until the treatment code was broken.

ii) This randomized study compared the efficacy of omeprazole at daily (o.m.) doses of 20mg and 10mg to placebo in patients treated for four weeks, for the symptoms of gastroesophageal reflux disease in the absence of erosive esophagitis.

iii) The primary endpoint was complete resolution of heartburn symptoms during the fourth treatment week, defined as no heartburn for seven days during this week. The original statistical methodology was a Mantel-Haenszel Chi-Square test, stratified by center.

The design included a 24-hour pH monitoring. To further describe the effect of omeprazole on patients with pathologic gastroesophageal reflux, Astra Merck reanalyzed the primary efficacy variable in those patients who had pH values < 4 in the distal esophagus for at least 4% of the pH monitoring time. This was done because

patients with normal esophageal acid exposure were not as likely to respond to the same degree as patients with acid related symptoms. The statistical methodology was a Mantel-Haenszel Chi-Square test, with Bonferroni adjustment for the three treatment comparisons, but no stratification by center. The normal approximation was used to compute 95% confidence intervals.

iv) inclusion criteria: at least 18 years old, heartburn as predominant reflux symptom for at least the last 12 months, and episodes of heartburn on at least 2 days during the last 7 days. The exclusion criteria are in appendix Table 1.

b) Sponsor's Analyses and Results

i) The actual number of patients enrolled is shown in Table A, following. Once a patient received study drug, at least 95% (Placebo) continued for the four week course, so the dropout rate is low. The four week rescue (four weeks open label treatment for patients without resolution) is included for completeness, with a placebo rescue rate of nearly double either omeprazole rate showing why the overall efficacy result is so strong.

Table A
Four Week Rescue/Completers/Treated (Completers/Treated %)

Omeprazole 20mg	Omeprazole 10mg	Placebo
72/196/205 (96%)	94/195/199 (98%)	73/100/105 (95%)

ii) The sponsor has not indicated that Intent-to-Treat (ITT) or All-Patients-Randomized (APR) analysis of I-1601 was done.

All Patients Treated (APT) analysis was done, as was Per Protocol (PP), analysis of patients complying well with the protocol. The main hypothesis being tested is whether the drug is effective in patients regardless of baseline esophageal acidity, per the following Table B. Assuming reasonable internal replicability, this reviewer feels a two-sided p-value not exceeding $p = .001$ is persuasive to a degree comparable to two trials each with two-sided p-values not exceeding $p = .05$. This criteria is met consistently for either dose of omeprazole versus placebo. With $p = .002$ and $p = .003$, the hypothesis that 20mg omeprazole is more effective than 10mg omeprazole is strongly suggested, but the statistical evidence is not as strong, and confirmation might be helpful.

Table B
Patients with Complete Resolution of Heartburn at Week 4
Primary Endpoint, from V100.3 pg 8-00057

	Normal Approximation Incidence(%) [95% CI]	Mantel-Haenszel p-value vs 20mg
All Patients Treated		
Omeprazole 20mg	95/205 (46%) [39%-53%]	
Omeprazole 10mg	62/199 (31%) [25%-38%]	p=.002
Placebo	14/105 (13%) [7%-20%]	p<.001
Per Protocol (Compliant)		
Omeprazole 20mg	90/189 (48%) [40%-55%]	
Omeprazole 10mg	60/186 (32%) [26%-39%]	p=.003
Placebo	14/100 (14%) [7%-21%]	p<.001

10mg beats placebo by p=.001 in both APT and PP analyses.

Rather than examining the internal replicability of study I-1601 beyond the Breslow-Day test results, this reviewer cites a second study of omeprazole 20mg versus placebo, in the following **Table C**. Per FDA request, the sponsor did a new analysis so the analyses of I-1601 and I-684 would be comparable, submitting the results with data on disk.

Table C
Different Study: I-684/569728
Patients with Heartburn Relief at Week 4
from supplement of 10/24/1996

	Incidence(%)	p-value vs 20mg
Intent-to-Treat		
Omeprazole 20mg	50/ 98 (51%)	
Placebo	18/111 (16%)	p<.001
All Patients Treated		
Omeprazole 20mg	50/ 87 (57%)	
Placebo	18/ 95 (19%)	p<.001

Next, in **Table D**, we see the efficacy for the subset with acid in the esophagus (pH <4 for >=4% of time monitored). Despite the smaller sample size, 20mg beats placebo handily, so we would certainly not conclude that the drug is less effective in patients with acid in the esophagus.

Table D
Patients with Complete Resolution of Heartburn at Week 4
and pH less than 4 for 4% or more of the time monitored
Primary Endpoint, from V100.3 Tables E-1,E-2

	Normal Approximation Incidence(%) [95% CI]	Mantel-Haenszel p-value vs 20mg
All Patients Treated		
Omeprazole 20mg	64/115 (56%) [47%-65%]	
Omeprazole 10mg	39/109 (36%) [27%-45%]	p=.003
Placebo	8/59 (14%) [5%-22%]	p<.001
Per Protocol (Compliant)		
Omeprazole 20mg	61/110 (56%) [46%-65%]	
Omeprazole 10mg	38/104 (37%) [27%-46%]	p=.006
Placebo	8/57 (14%) [5%-23%]	p<.001

10mg beats placebo by p=.002 and p=.003 respectively.

There was a slight imbalance regarding gender and smoking between the treatment groups. To evaluate the impact of these factors on complete relief of heartburn, a logistic regression model was used with treatment, gender and smoking as explanatory variables on the Per Protocol population. The results showed that the estimated treatment effects did not change much and were still statistically significant. Smoking reached a p-value of p=.10 and gender reached p=.40.

The Breslow-Day test was used to evaluate possible center effects, with no indication of inhomogeneity among centers regarding the effect on complete relief of heartburn (p>.15 for all three comparisons, in APT and PP analyses, acidic and normal patients together.)

Subset analyses by age, gender and evaluating center were done, shown in the following **Table E**. Elderly (over 65 years) patients numbered 78, at 15% of the patient population. The sponsor submitted a supplement dated 8/29/1996 to address the lower overall healing rates in I-1601 relative to four other trials, attributing the difference to differences in age and gender between trials; young women having a lower response rate. The design of I-1601 is parallel and concurrent, so the hypothesis of age and gender effects on the overall response rate does not affect this reviewer's inferences regarding treatment effect.

Table E
Patients with Complete Resolution of Heartburn at Week 4
Primary Endpoint, from V100.3 Tables E-5, E-6
Subsets by Gender and Age

	————— (% resolved) # at risk —————		
	Omeprazole 20mg	Omeprazole 10mg	Placebo
All Patients Treated			
Male	(56%) 66	(30%) 89	(14%) 51
Female	(42%) 139	(32%) 110	(13%) 54
All Patients Treated			
18-49 years	(42%) 94	(24%) 107	(11%) 46
50-64 years	(45%) 73	(37%) 70	(15%) 41
≥65 years	(61%) 38	(46%) 22	(17%) 18
pH <4, >4% of time			
Male	(63%) 40	(33%) 52	(14%) 29
Female	(52%) 75	(39%) 57	(13%) 30
pH <4, >4% of time			
18-49 years	(47%) 51	(30%) 47	(14%) 22
50-64 years	(62%) 39	(36%) 44	(17%) 24
≥65 years	(64%) 25	(50%) 18	(8%) 13

Subset analysis by race was not done since only 4 out of 509 patients were not Caucasian.

Overall, 20mg omeprazole is more efficacious than placebo.

Intake of less than 75% of the medication that should have been taken during the period was considered as inadequate compliance but was not a reason for discontinuation. The patients were provided with antacid (Novalucol Novum) for episodic rescue.

III. REVIEWER'S COMMENTS AND CONCLUSIONS

The design of the protocol seems very good. The firm was careful in small points such as having central briefing of investigators regarding the protocol and keeping the randomization block size blinded. This reviewer did not find any problems in the conduct of the trial.

The sponsor applied the Breslow-Day test to search for treatment by center interaction at the $p = .15$ level, as this reviewer would wish. No evidence of treatment by center interaction was found.

With $p < .001$ from appropriate statistical methodologies applied to the primary endpoint for 20mg omeprazole versus placebo, further supported by I-684, there is a clear result for efficacy of 20mg omeprazole versus placebo. This reviewer has no objection to including summary results of I-1601 in the label.

The p-values for 10mg omeprazole versus placebo appears adequate to show efficacy from a single trial, since the Breslow-Day test did not find treatment by center interaction. On its face, the patients appear reasonably evenly distributed between the centers.

The p-values for 20mg omeprazole versus 10mg omeprazole are significant at the 0.05 level, per **Tables B and D**, but might benefit from confirmation by a second trial. The label seems to imply "significance within the context of one trial", not necessarily implying that practicing clinicians will find a significant difference in their own patients, so this reviewer has no objection to this portion of the relabeling (see page 2 of this review.)

This reviewer is unsure of the reasons for first line treatment versus second line, so this is addressed only through the question of efficacy in this review.

OVERALL CONCLUSION

Based on the statistical evaluation of efficacy, this reviewer has no objections to the relabeling requested.

Ferrin Harrison 11/25/1996

Ferrin Harrison, Ph.D.
Mathematical Statistician

This review consists of 8 pages of text, and 1 page of appendix table.

Concur: Dr. Huque, Ph.D.
Team Leader

M J Huque 11/25/96

Dr. Smith, Ph.D.
Division Director

A Smith 11/25/96

cc: Archival NDA

HFD-180/ Division Files
HFD-180/ Dr. Fredd
HFD-180/ Dr. Gallo-Torres
HFD-180/ Ms. Walsh
HFD-720/ Dr. Smith
HFD-720/ Dr. Huque
HFD-720/ Dr. Harrison
HFD-720/ Chron
HFD-720/ File Copy

HFD-720/HARRISONF/11-25-1996/wp61/OMEPS36.DOC

Table 1
Exclusion Criteria
Source: V100.3, Clinical Study Report

1. Presence or history of macroscopic erosive and/or ulcerative esophagitis, and/or peptic ulcer in the stomach or duodenum.
2. Esophageal stricture and/or Barrett's esophagus.
3. Symptoms indicating complications of GERD (e.g. melaena, haematemesis).
4. History of esophagogastric surgery except for simple closure of perforations.
5. Pregnancy or lactation.
6. Concurrent disease (past or present) likely to complicate the evaluation of study treatment, e.g. significant cardiovascular, renal or hepatic disease, or malignancy.
7. Clinically significant abnormal values in the pre-study laboratory screen as judged by the investigator, other than those directly related to some concurrent and stable disease.
8. Treatment with any investigational compound within the previous month.
9. Treatment with antisecretory agents (e.g. H2-receptor antagonists or proton pump inhibitors) in ulcer healing doses within the month prior to endoscopy.
10. Requirement of an interpreter.
11. Alcohol or drug abuse or any conditions associated with poor compliance.
12. Previous enrolment in the study.

(Failure to give signed or witnessed verbal informed consent to participate in the study.)

1020571 JAN - 5 1996

CHEMIST'S REVIEW 1		1. Organization: HFD-180	2. NDA Number: 19-810
3. Name and Address of Applicant (City & State): Astra Merck Group 725 Chesterbrook Boulevard Wayne, Pennsylvania 19087-5677		4. AF Number:	
6. Name of Drug: Prilosec		7. Nonproprietary Name: omeprazole	5. Supplement Numbers Dates SE1-036 May 14, 1995
8. Supplement Provides for: for use of Prilosec treatment of symptoms of Gastroesophageal Reflux Disease (GERD) in patients who do not show evidence of erosive esophagitis and who have not necessarily failed to respond to other therapeutic options.		9. Amendments and Other (Reports, etc.) Dates: RS December 27, 1995	
10. Pharmacological Category: anti-ulcer	11. How Dispensed: RX <input checked="" type="checkbox"/> OTC <input type="checkbox"/>	12. Related IND/NDA/DMF(s):	
13. Dosage Form: capsule (delayed release)	14. Potency: 10 and 20 mg	16. Records and Reports: Current Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Reviewed Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
15. Chemical Name and Structure: See USP Dictionary of USAN, 1995 edition, Page 485.		17. Comments: EA Review attached. cc: NDA 19-810/SE1-036 HFD-180/Div File HFD-181/CSO HFD-180/SFredd HFD-180/AShaw R/D init: JGibbs/1-4-96 ABS/dob F/T 1-4-96\Wp: c:\wpfiles\chem\S\19810036.1AS	
18. Conclusions and Recommendations: The EA is acceptable and a FONSI should be prepared.			
19. Reviewer			
Name: Arthur B. Shaw, Ph. D.	Signature <i>Arthur B Shaw</i>	Date Completed: January 3, 1996	<i>JGibbs</i> 1/5/96

11/10/86

ENVIRONMENTAL ASSESSMENT

AND

MAR - 7 1986

FINDING OF NO SIGNIFICANT IMPACT

FOR

**PRILOSEC® Delayed Release Capsules
(omeprazole)**

NDA 19-810/S-036

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

**DIVISION OF GASTROINTESTINAL AND
COAGULATION DRUG PRODUCTS (HFD-180)**

**PRILOSEC® Delayed Release Capsules
(omeprazole)**

NDA 19-810/S-036

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for **Prilosec, Astra/Merck** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the incremental increase in manufacture, use, and disposal of the product that will result from approval of the additional treatment indication requested in the supplemental application.

Omeprazole is a synthetic drug which is currently administered orally for the treatment of a number of gastrointestinal diseases. The drug substance will be manufactured at the Merck Manufacturing Division facility in Albany, Georgia. The drug product will be manufactured, encapsulated and packaged at the Merck Manufacturing Division facilities at Arecibo, Puerto Rico, Kirkland, Canada, West Point, Pennsylvania, and Wilson, North Carolina. The finished drug product will be used on an in-patient and out-patient basis in the United States.

Approval of the drug product covered by this supplemental application will not result in any change in the chemicals or processes used in the production of the capsules. There is expected to be a change in the amount of drug marketed if the application is approved, therefore it was necessary to evaluate the environmental impact of the increased quantities of drug substance which may enter the environment. The amount of drug expected to be emitted into the environment if the application is approved is expected not to be significant.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. No effects upon endangered species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

1/4/96 Arthur B. Shaw
DATE Prepared By
Arthur B. Shaw, Ph.D.
Review Chemist
Division of Gastrointestinal and Coagulation Drug
Products

1/5/96 John J. Gibbs
DATE Division Concurrence
John J. Gibbs, Ph.D.
Supervisory Chemist
Division of Gastrointestinal and Coagulation Drug
Products

3/7/96 Nancy B. Sager
DATE Concurred
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment I: EA ~~Review~~

CC: Original NDA 19-810/S-036
HFD-004/FONSI File 19-810/S-036
HFD-004/Docket File
HFD-019/FOI Copy
HFD-180/AShaw
R/D init.:JGibbs/1-4-96
ABS/dob_F/T 1-4-96\WP: c:\wpfiles\chem\S\19810036.2AS

Environmental Assessment - Redacted Version

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Omeprazole Capsules
Chemical and Pharmaceutical Manufacturing and
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1. Date

August 25, 1995

2. Name of Applicant

Astra Merck

3. Address

725 Chesterbrook Blvd.
Wayne, PA 19087

4. Description of the Proposed Action

a. Requested Action

Astra Merck has filed a Supplemental New Drug Application for PRILOSEC capsules for the treatment of heartburn and other symptoms associated with Gastroesophageal Reflux Disease (GERD). This environmental assessment evaluates the changes in patient use and manufacturing changes at the Merck & Co., Inc. sites located in Albany, Georgia; Arecibo, Puerto Rico; Kirkland, Canada; and West Point, Pennsylvania and packaging sites in Arecibo, Puerto Rico and Wilson, North Carolina. These are the principal sites where incremental increases are projected as the result of the proposed action. The extent of the evaluation provides a comparison of maximum expected environmental concentrations (MEECs) and the environmental fate and effects data in the previously approved PRILOSEC Supplemental New Drug Application for (NDA 19-810) dated January 17, 1991.

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b. Need For Action

PRLOSEC offer patients with gastroesophageal reflux disease (GERD) an effective therapy for its management. Because of the therapeutic benefits associated with its availability and use, approval is justified and preferable to non-approval.

Drug substance quantities needed to support 5th year marketing for all of the extended release products in the United States are approximately kg/year of omeprazole. Of that kg/year, approximately kg/year of omeprazole would be needed to support this GERD claim.

c. Locations Where the Product will be Produced and the Types of Environments Adjacent to Those Locations

Omeprazole bulk drug substance will be manufactured by the Merck Manufacturing Division facility in Albany, Georgia. The drug product will be manufactured and encapsulated at the Merck Manufacturing Division facilities in Arecibo, Puerto Rico; Kirkland, Canada; and West Point, Pennsylvania. The capsules will be packaged at the Merck Manufacturing Division facilities in Arecibo, Puerto Rico and Wilson, North Carolina. Returned and outdated drug-related materials will be disposed of at the Merck West Point, Pennsylvania facility.

Environments present at the Merck locations mentioned above, specific to drug substance manufacture and drug product manufacture, encapsulation and packaging are described in the following sections.

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1) Albany, Georgia

a) Geographic Conditions

The Albany, Georgia plant occupies approximately 780 acres in Dougherty County, Georgia on the west side of Georgia Route 3, approximately 0.5 miles east of the Flint River. It is situated approximately five miles south of the city of Albany, Georgia. The coordinates of the plant's location are latitude 31° 29' N and longitude 84° 7' W. Annual rainfall in the area is approximately 49 inches (124.5 cm). The mean summer temperature is 92° F (33° C), while the mean winter temperature is 42°F (5.6 °C). Dougherty County, which includes the city of Albany, has an approximate population of 125,000.

b) Air Resources

The entire state of Georgia is in attainment with the National Ambient Air Quality Standards (NAAQS) for particulates, sulfur oxides, and nitrogen oxides. The plant is located in the southwest Georgia Intrastate Air Quality Control region which is in attainment with the secondary standards for carbon monoxide and ozone. The state of Georgia has been delegated authority to enforce new and existing air pollution regulations including the New Source Performance Standards (NSPS), National Emission Standards for Hazardous Air Pollutants (NESHAPS), and Prevention of Significant Deterioration (PSD). There are no Class I visibility areas within 50 km of the plant.

c) Water Resources

The plant obtains its potable water from two on-site wells. All process and non-contact cooling water is obtained from six other on-site wells. The

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c) Water Resources (Con't)

plant has been issued two permits from the Georgia Department of National Resources for the above referenced well water. Withdrawal of groundwater from these wells is authorized by Permit Number 0470003. The treatment and distribution of drinking water is authorized by Permit Number PG0950023.

The only surface water body within 1000 ft. of the plant property boundary is the Flint River which is approximately 0.2 miles west of the plant area.

d) Land Resources

The land use of the area surrounding the plant site is primarily undeveloped and agricultural with low density residential housing to the north and east. The closest major population center is the city of Albany approximately five miles to the north.

The 100-year flood-plain elevation at the site is approximately 179 feet above mean sea level. All existing buildings and improvements are located above this elevation.

2) Arecibo, Puerto Rico

a) Geographic Conditions

The Merck Sharp & Dohme Quimica de Puerto Rico Inc. (MSDQ) Arecibo facility is located on an 18.45 acre site in the Sabana Hoyos Ward of the Municipality of Arecibo. The 60 kilometer marker of the De Diego Expressway (PR-2) lies to the north.

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a) Geographic Conditions (Con't)

The coordinates of the facility location are latitude 14° N and longitude 66.45° W. Approximately 500 people live within a half mile radius of the facility.

b) Air Resources

Annual rainfall is approximately 60 inches and the mean ambient temperature varies between 76 and 82°F. An easterly trade wind is the predominant wind pattern.

The MSDQ Arecibo facility is located in the Barceloneta air basin which is in attainment with the National Ambient Air Quality Standards (NAAQS) for all criteria pollutants. The commonwealth requires both new source permits and operating permits for all point sources. Puerto Rico is part of USEPA Region II and has been delegated authority over the National Emissions Standards for Hazardous Air Pollutants Program (NESHAPS). Meteorological data for the area is collected at the Isla Verde Airport in San Juan (about 50 miles east of the MSDQ-Arecibo facility).

c) Water Resources

All water used for consumption, process and sanitary equipment is supplied by an on-site artesian well. The Department of Natural Resources of Puerto Rico issued a permit on December 11, 1990 (Permit No. PPA-121-90) which allowed for the construction of a well which is capable of extracting 1,000,000 gallons per day (GPD) of water from the artesian aquifer. The depth of this aquifer varies from 800 to 1,700 feet depending on the topography of the area. The facility has a deep well franchise agreement issued on July 24, 1991 (Franchise No. FP-197-91) from the

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c) Water Resources (Cont')

Department of Natural Resources which allows the extraction of 100,000 GPD.

The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Separate sewer systems exist for sanitary, process, and storm water runoff. The domestic/sanitary waste is discharged to the south of the site, into the Puerto Rico Aqueduct and Sewer Authority (PRASA) sewage system. The process sewer line joins with the sanitary sewer at the metering pit prior to discharge to the PRASA sewage system. The wastewater treatment plant is the Barceloneta Regional Wastewater Treatment Plant (BRWTP) located in Barceloneta, approximately 5 miles from the plant (NPDES Permit Number PR0021237). The final discharge (combined process and sanitary sewage) is subject to conditions specified in an industrial discharge permit with PRASA, effective June 30, 1994.

Storm water from the plant is collected in an independent sewer system. Surface water runoff from portions of the plant discharge to the drainage basin on the south side of the site.

There is one injection well on the plant property. It is located in the drainage pit on the south side of the site. It is only used for stormwater when the stormwater influx into the drainage pit exceeds the volume of the drainage basin.

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c) Water Resources (Con't)

There are no surface water bodies in the vicinity of the area. Due to geologic conditions of the Zone, the drainage is mainly underground. The Atlantic Ocean is approximately 3 miles to the north of the site.

d) Land Resources

Land use surrounding the plant is mixed. The De Diego Expressway (PR-2) is located to the north of the site. Adjacent to the south side of the site, is another pharmaceutical company. Surrounding the site to the east and west is a motel and pineapple farm, respectively.

The regional geology (Barceloneta Quadrangle) is composed of sedimentary rocks, of Tertiary or Quaternary age. These sedimentary rocks are overlain by Quaternary deposits composed of alluvial, beach, swamps, landslide and lagoonal deposits with artificial fill.

In general, the sedimentary rocks consist of limestone, chalk and marl. At many localities, the bedrock is concealed by the surficial deposits, the result of mass movement and/or chemical weathering. Most of the unconsolidated deposits comprise gravel, sand, clay, and silt, also some peat and peaty muck and artificial fill deposits may be present at the flood plains.

The nearby site geology is underlain by sedimentary rocks. These geologic formations are known as Camuy, Aymamon and Aguada Limestones, respectively.

The outcropping geologic formation at the site comprises blanket deposits which rest on the valleys between the limestone hills over the older

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b) Air Resources (Cont)

Environment Department of the "Communaute Urbaine de Montreal." The Kirkland facility is in compliance with this regulation.

The annual rainfall is approximately 723 mm and the annual snowfall is approximately 235 cm (1991 data) The annual temperature ranges from a minimum of -30°C to a maximum of 36°C. Prevailing winds are from the southwest at an average annual speed of 15 km/h.

c) Water Resources

Potable water is obtained from the water board "Communaute Urbaine de Montreal". The plant potable water quality meets all requirements of the Provincial regulations. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Wastewater from the facility is routed to the publicly owned treatment works - "Communaute Urbaine de Montreal" for treatment. The discharge to the treatment plant is monitored twice a year according to the parameters under the Communaute Urbaine de Montreal regulation.

d) Land Resources

The plant site is primarily flat. A glacial till knob exists on the east side of the property and this till layer slopes down beneath the flat deep clay deposit toward the west. The soils are therefore quite variable across the site but consist primarily of a shallow sand and gravel layer at the ground surface, followed by brown clay with sand layers. Below this zone, desiccated brown clay which changes to gray is present. The gray clay

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d) Land Resources (Con't)

extends down to clayey silt until large boulders or bedrock is encountered. The typical depth to bedrock is around 30 feet. The plant site elevation is about 153-175 meter above mean sea level.

4) West Point, Pennsylvania

a) Geographic Conditions

The West Point plant is located on a site (~450 acres) in Upper Gwynedd Township, Montgomery County, which is approximately 30 miles northwest of Philadelphia. The center of the West Point plant is located near latitude 40° 12' 54" N and longitude 75° 17' 59" W. Land use surrounding the plant is primarily residential and agricultural with other industrial sites approximately one-half mile away.

b) Air Resources

Air quality in this area is in compliance with the Environmental Protection Agency's (EPA) National Ambient Air Quality Standards (NAAQS) of the Clean Air Act for total suspended particulates, sulfur oxides, and nitrogen oxides. This compliance is based on monitoring and reporting by the Pennsylvania Department of Environmental Resources (PA DER) under the requirements of the State Implementation Plan. At this time, Montgomery County does not meet the ozone standard set forth by the NAAQS. The West Point plant lies within the outer zone of the Southeast Pennsylvania air basin. Pennsylvania is part of the EPA Region III and PA DER is responsible for implementing the State Implementation Plan which includes new stationary source permits for manufacturing. Meteorological data for the region is collected at the Philadelphia International Airport. Annual

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b) Air Resources (Con't)

rainfall is approximately 42 inches (107 cm) and the mean ambient monthly temperature varies between 33 and 77°F (0.5-25°C). Predominant winds are from west to southeast.

c) Water Resources

Potable water is supplied to the plant operations via an on-site storage tank which is supplied by on-site wells and a public water supplier, North Wales Water. North Wales Water Authority operates as many as three public wells within a half-mile of the plant property. The plant potable water quality meets all applicable requirements of the Federal Safe Drinking Water Act and the Pennsylvania Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices.

Stormwater drainage is controlled using detention basins which maintain site runoff at levels estimated for undeveloped property and to minimize erosion. This runoff is discharged into either the Towamencin Creek or the Wissahickon Creek.

Wastewaters generated as a result of formulation will be discharged to the Upper Gwynedd Township Wastewater Treatment Plant (UGTA WWTP). The UGTA discharges treated effluent to the Wissahicken Creek.

The location of the discharge from the UGTA is downstream from the West Point site. Pennsylvania DER limits the wasteload allocation and water pollutant limits (established by the Pennsylvania Water Toxics Management) from the UGTA by means of the National Pollutant

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c) Water Resources (Con't)

Discharge Elimination System discharge permit. This wasteload allocation and water pollutant limit are used to determine the allowable contribution limits from the West Point site. The treated wastewater is also regulated by the UGTA under permit and local ordinance.

d) Land Resources

The plant is underlain by Triassic age sedimentary rocks, mapped as the Brunswick and Lockatong formations. These formations occur as layered beds of red and very dark gray shale with occasional layers of sandstone. Although these rocks generally have low primary porosities, permeability is maintained and improved by the presence of fractures and joint sets.

The plant site elevation is about 361 feet above mean sea level (United States Geologic Survey datum).

5) Wilson, North Carolina

a) Geographic Conditions

Wilson is located 45 miles east of Raleigh, North Carolina. The plant is located 4.5 miles west of Wilson on a 225-acre plot, near the intersection of Interstate Highway 95 and Highway US 264, at latitude 35° 45' north and longitude 78° 00' west. Land use surrounding the plant is primarily residential and agricultural.

b) Air Resources

Air quality in the region meets the National Ambient Air Quality Standards (NAAQS) for sulfur oxides, nitrogen oxides, total suspended particulates

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b) Air Resources (Con't)

and ozone. The annual rainfall is approximately 42 inches, and the average annual temperature is 59°C. Prevailing winds are from the southwest at an average annual speed of 7.7 mph.

c) Water Resources

Potable water is obtained from the local public water supply for the city of Wilson. The plant potable water quality meets or exceeds all requirements of the Federal Safe Drinking Water Act. Compliance with these standards are also required in applicable Good Manufacturing Practices. Wastewater from the facility is routed to the city of Wilson treatment facility. In the developed area of the property, there are six natural drainage tributaries exiting the plant property and one entering the property. There is an established stormwater monitoring point for monitoring all stormwater releases from the plant site.

d) Land Resources

The plant site consists mainly of gently sloping terrain with forest and open farmland underlain by the Coastal Plain Providence to the east and the geologic Piedmont Geologic Providence to the west. The coastal plain soils are marine deposits and the piedmont soils are residual, formed from the chemical decomposition of the underlying bedrock. Both soils are interbedded sands, silts, and clays with the typical depth to bedrock 20-40 feet. The plant site elevation is about 160 feet above mean sea level.

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d. Locations where the Product will be Used and the Types of Environments Present at and Adjacent to those Locations

The product is intended for use throughout the United States for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease. Consumption will be on an in-patient and out-patient basis.

e. Locations where the Product will be Disposed of and the Types of Environments Present at and Adjacent to those Locations

Merck & Co., Inc. has a domestic return goods policy which involves the return of any unused market packages to the West Point, Pennsylvania location for evaluation and disposal. The product is disposed of at the West Point facility by incineration or an approved off-site facility, and any ash generated is landfilled at a permitted off-site facility. This essentially results in a single location for control of product disposal. The types of environments present at the disposal plant site are described in Section 4.c.4.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

Information concerning the chemical structure, empirical formula, molecular weight, chemical name, laboratory codes, generic name, trade name and CAS (Chemical Abstracts Service Registry) number for omeprazole can be found in Appendix I.

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6. Introduction of Substances Into the Environment

a. Substances expected to be emitted and estimated releases

1) Bulk drug synthesis

Part 2 of Appendix II summarizes the chemical substances which may be expected to enter various environmental compartments (atmospheric, aquatic and terrestrial) as a result of bulk production. Production of omeprazole will take place at Merck's facility in Albany, Georgia. The scope of this environmental assessment only covers the incremental increase in production of omeprazole at the Albany, Georgia facility to supply marketing requirements for this GERD claim.

2) Dosage Form Production

The drug product manufacturing operations for the Arecibo, Puerto Rico; Kirkland, Canada; and West Point Pennsylvania production sites involve the preparation of an aqueous-based granulation of the drug substance and common USP/NF pharmaceutical excipients. The granulation is extruded and marumerized into pellets, dried, and subcoated. The subcoated pellets are enteric coated and encapsulated. Packaging of capsules will occur at the Arecibo, Puerto Rico and Wilson, North Carolina sites. See Part 3 of Appendix II which summarizes information describing the substances which may be emitted as a result of dosage form production. The scope of this environmental assessment only covers the incremental increase in formulation of omeprazole at the Arecibo, Puerto Rico; Kirkland, Canada; and West Point, Pennsylvania facilities to supply marketing requirements for this GERD claim.

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3) Use Sites

Administered dosage form will normally enter the environment in highly diluted aqueous domestic sewage which will be subject to further local treatment. The maximum expected emitted concentration (MEEC) resulting from the use of all omeprazole products is estimated to be approximately mcg/L (ppb) based on projected fifth year production levels for the U. S. market for omeprazole. The incremental MEEC resulting from the use of omeprazole for this GERD indication is estimated to be only mcg/l (ppb). These estimates assume that 74% of the total drug administered will be discharged in domestic sewage (reflects the fraction of the US population which discharge sanitary waste to Publicly Owned Treatment Works, a uniform distribution throughout the U. S. population, a per capita water usage of 150 gallons per day, and excretion of 100% of drug activity. Lifetime exposure to this concentration for this GERD claim would result in ingestion of less than one mg dose. Use of the drug is not expected to result in emissions to the atmospheric or terrestrial compartments.

4) Disposal Sites

The Merck West Point, Pennsylvania incineration facilities will be used to treat return product. On-site incineration facilities will handle the majority of this waste with resulting releases limited to less than 0.1% of throughput. In the event that the West Point facility is unable to accept such waste, the wastes will be disposed of at an alternate permitted off-site facility. The expected emissions from the disposal site are described below.

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4) Disposal Sites (Con't)

- i) Air Emissions - Particulates and vapors (carbon dioxide, water vapor, etc.) are expected to be emitted into the atmosphere from the incineration operation of returned goods. The on-site West Point facility incineration operation is in compliance with all applicable standards and permit limits. Any off-site incineration will be conducted at an equivalent, permitted facility.
- ii) Liquid Emissions - Any wastewater generated from the incinerator operation will be discharged into the sanitary sewer which undergoes on-site pretreatment for equalization and is discharged for off-site biological wastewater treatment at the UGTA.
- iii) Solid Emissions - All returned and outdated market packages and residual omeprazole waste from operations at West Point will be incinerated at on-site or off-site facilities permitted to handle such waste streams.
- iv) Employee Protection - Employee protective clothing such as gloves, uniform, and safety shoes and protective equipment such as safety glasses and respirators are used when required for handling purposes to assure compliance with The Occupational Safety and Health Act of 1971. Copies of the MSDSs are available to all employees for all compounds relevant to drug product manufacture, including the drug substance. Refer to Appendix IV for the omeprazole MSDS.

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b. Control Procedures and Citations of Compliance

1) Albany, Georgia

a) Air Emissions Controls and Citations - Bulk Drug Substance

Air emissions from bulk manufacture of omeprazole may include organic and inorganic substances identified in part 2 of Appendix II. The emissions will be controlled by equipment such as process condensers, a fume incinerator and wet scrubbers, where necessary, so that the facility complies with applicable air emission permits.

A dust collector will be used to control the atmospheric release of total suspended particulate matter in the milling process for the drug substance with a control efficiency of >99%, however, trace quantities of product dust may be emitted. Particulate emission rates will be less than the allowable emission rate based on the process charge rates for new and existing equipment specified in the Georgia Rules for Air Quality Control Chapter 391-3-1-.02(2)(e) Table Ia and Ib. For example, a typical process charge rate of less than or equal to 100 lb/hr has an associated emission rate of 0.55 lb/hr.

Air emissions are subject to and in compliance with the rules of the Georgia Department of Natural Resources, Environmental Protection Division, Chapter 391-3-1, Air Quality Control. Air emissions are discharged subject to the Air Quality Permit Number 2833-047-10356 and 2833-047-11517, as amended.

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a) Air Emissions Controls and Citations - Bulk Drug Substance (Con't)

Particulate emissions from the manufacture of drug substance are subject to and in compliance with the emission rates set forth by regulation under Table Ia and Ib, Chapter 391-3-1-.02(2)(e), for new and existing equipment. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new regulation parameters are anticipated as a result of the proposed action.

b) Liquid Emissions Controls and Citations- Bulk Drug Substance

The plant has separate sanitary, process and stormwater sewer systems. All process and sanitary wastewater from laboratory, production and administration areas are sent to the on-site wastewater treatment plant. The treatment plant consists of the following processes: equalization, neutralization, primary clarification, activated sludge, secondary settling, thickening, sludge dewatering and off-site sludge disposal.

The stormwater collection system is equipped with a deluge containment to collect any spills and allow subsequent rerouting to the wastewater treatment plant. Uncontaminated stormwater may be discharged directly to the Flint River.

Organic liquid waste streams generated from the manufacture of drug substance will be subject to on-site recovery of the organic solvents to the extent practicable. Residues from the solvent recovery operations are sent to the plant's wastewater treatment plant or, if necessary, shipped off-site to a permitted hazardous

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b) Liquid Emissions Controls and Citations- Bulk Drug Substance (Con't)
waste management facility.

The remaining organic liquid waste streams are sent off-site for incineration or fuels blending to facilities authorized and permitted to handle these waste streams.

Aqueous waste streams generated from the manufacturing of drug substance will be sent to the on-site wastewater treatment facility as described above prior to discharge to the Flint River. Chemical substances that may be discharged to wastewater treatment are listed in Part 2 of Appendix II.

Effluent from the on-site wastewater treatment plant is discharged to the Flint River and is subject to and in compliance with the National Pollutant Discharge Elimination System (NPDES) Permit Number GA0001619. The NPDES permit is administered by the Georgia Department of Natural Resources. The existing NPDES permit limits plant effluent to a BOD₅ daily maximum of 2,100 lb/day (June-Oct.), 4375 lb/day (Nov. - May); TSS daily maximum of 4,200 lb/day and pH between 6.0 and 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Emissions Controls and Citations- Bulk Drug Substance

Wastewater treatment plant sludge is containerized and shipped off-site to a permitted hazardous waste management facility. RCRA

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c) Solid Emissions Controls and Citations- Bulk Drug Substance (Con't)

non-hazardous waste including paper trash and non-hazardous filter media generated from the production of drug substance will be shipped off-site to a permitted local landfill. Empty containers are re-sold or sent to a drum reconditioning facility to the maximum extent practical.

Hazardous solid waste is subject to, and conforms with the Georgia Hazardous Waste Management Rules, Chapter 391-3-11, Standards Applicable to Generators of Hazardous Waste. The USEPA hazardous waste permit identification number for the plant is GA0003324985. The plant has a RCRA permit for the storage of hazardous waste in tanks and containers (permit no. HW008(S)). There are no numerical permit limits associated with the manufacture of omeprazole at the Albany facility although efforts will be made to minimize the amount of solid waste generated. No new permit conditions are anticipated as a result of the proposed action.

d) Employee Protection

Material Safety Data Sheets (MSDS) are available on-site for all chemicals required by the Occupational Safety Act of 1971 and the Hazards Communication Act of 1985. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. The MSDS for omeprazole is contained in Appendix IV. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing

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d) Employee Protection (Cont)

process to assure compliance with the Occupational Safety Act (OSHA) of 1971 and the Hazards Communication Act of 1985.

2) Arecibo, Puerto Rico

a) Air Emissions Controls and Citations - Drug Product Formulation

Air emissions from drug product formulation may include the substances listed in Part 3 of Appendix II.

The acetone and ethanol air emissions resulting from the coating process will be directly vented and controlled by a >99% efficient thermal incinerator. The incinerator will be permitted to comply with all USEPA and local regulations which require less than 3 lbs/hour and 15 lbs/day of solvent emissions. Dust collectors utilizing HEPA filters will ensure particulate emission control. Approval of the proposed action will not impact the facility's ability to comply with all applicable air emission requirements.

b) Liquid Emissions Controls and Citations - Drug Product Formulation

A mixture of acetone and 95% ethanol is used to coat the pellets. The solvent waste will be drummed and transported by a licensed carrier to a permitted incinerator or fuel blending facility for disposal, eliminating any impact this waste stream could have on the receiving wastewater treatment plant.

No other solvents are used in the formulation process. Liquid wastes will result from equipment cleaning. Equipment will be

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b) Liquid Emissions Controls and Citations - Drug Product Formulation
(Cont)

vacuumed prior to water washing to remove residual product and excipients such as lactose, mannitol, and microcrystalline cellulose. Therefore, the quantity of residual product and excipients resulting in wastewater will be minimal. Due to the drug's highly unstable photolytic and hydrolytic nature, the discharge to the environment will have minimal environmental impact.

The effluent from the Arecibo site is treated by the Barceloneta Regional Wastewater Treatment Plant (BRWTP), and this effluent is discharged from the BRWTP under NPDES Permit Number PR0021237. This permit is administered by the Puerto Rico Aqueduct and Sewer Authority (PRASA). The wastewater is subject to the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439. The site wastewater is regulated by an industrial permit #GDA-93-202-052 effective June 30, 1994 with an expiration date of June 30, 1995. The site continues operation under the existing permit until the agency issues a new permit. This permit limits the site average daily wastewater discharge to a biological oxygen demand (BOD5) of 900 mg/l, total suspended solids (TSS) of 250 mg/l, and pH of 7.5 to 9.0. Chemical substances that may be discharge into the wastewater are listed in Part 3 of Appendix II.

Approval of the proposed action will not impact the facility's ability to comply with the conditions of the wastewater agreement.

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b) Liquid Emissions Controls and Citations - Drug Product Formulation

(Con't)

The underground injection well is permitted with the Environmental Quality Board (UIC Permit Number 84-0191) and is in compliance with the provisions of the Public Policy Environmental Act (Law No. 9), and the Underground Injection Control Regulation. All discharges to the well will be stormwater and will be in compliance with the permit.

c) Solid Waste Controls and Citations - Drug Product Formulation

Dry solid waste (e.g. paper, HEPA filters, dusts, tablets, etc.) from omeprazole drug product formulation will be transported by a licensed carrier to a permitted incinerator for disposal. No hazardous solid waste will be generated by the production process.

Solid waste management at the Arecibo plant required conformance with conditions set forth by the Environmental Quality Board (EQB). The EQB has the authority to regulate solid waste management. Hazardous and non-hazardous wastes in Puerto Rico are regulated by the Public Policy Environmental Act (Law No. 9), and the Regulation for the Control of Hazardous and Non-Hazardous Wastes (Solid Waste Regulation). These requirements assure comprehensive control for the management of waste throughout the plant including returned market packages that are sent to West Point for disposal. These regulations are subject to the requirements of the Federal Resource Conservation

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c) Solid Waste Controls and Citations - Drug Product Formulation (Con't)

and Recovery Act, the Federal Hazardous and Solid Waste Amendments. These regulations do not limit the quantity of solid waste generated. However, recycling will be implemented to the fullest extent possible to minimize the amount of solid waste generated. Currently, the facility has no solid or hazardous waste permits and none are required for approval of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug substance.

To minimize worker exposure to omeprazole, periodic monitoring of dust levels will be performed where omeprazole powders are handled. To minimize worker exposure to the acetone and ethanol periodic air monitoring of organic vapors will be performed where the solvents are handled.

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3) Kirkland, Canada

a) Air Emissions Controls and Citations - Drug Product Formulation

Air emissions from manufacture and packaging may include trace particulates as described in Appendix II. Particulates leaving the coating column are presently controlled by a wet dust collector. The wet dust collector is approved by the Director of the Environment Department of the "Communaute Urbaine de Montreal." A project involving the installation of a thermal oxidizer to control particulates and solvent emissions is in progress. As required, a permit will be obtained for this equipment prior to installation.

The operation of the Kirkland manufacturing and packaging operations is allowed and is in compliance with regulations respecting the quality of the atmosphere (Provincial Regulation) and MUC By-Law 90 pertaining to air purification. This air legislation for Quebec limits the emission of various pollutants into the atmosphere. These pollutants include different types of chemicals, smoke, sulfur, particulates, etc. Any source that emits these pollutants is subject to the approval of the Director of the Environment Department of the "Communaute Urbaine de Montreal." The incinerator and wet dust collectors are subject to and in compliance with this legislation. The permit for incinerator #201-09-00-09-92-3580D003 requires continuous monitoring for O₂, CO, CO₂, and particulates. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

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b) Liquid Emissions Controls and Citations - Drug Product Formulation

The plant wastewater is collected and routed directly to the municipality, as regulated under the discharge permit #348. This permit, along with the municipal discharge regulation (By-Law 87), limits the quantity of pollutants to be discharged and also specifies reporting requirements for spills. The permit limits include pH 6-10.5, temperature < 65°C, and Oil and Grease <150 mg/l.

The liquid emissions resulting from the drug product manufacture and packaging will contain constituents listed in Part 3 of Appendix II. Liquid waste from manufacturing, filling, and packaging will result from equipment washouts and solvent coating residual. Equipment is cleaned with detergent and water after a batch campaign. The wastewater discharged to the wastewater treatment plant will comply with the site permit limits stated above.

No new permit limits are anticipated as a result of the proposed action. Approval of this submittal will not impact the facility's compliance with the site wastewater discharge permit.

c) Solid Waste Controls and Citations - Drug Product Formulation

Any solid residuals that contain active drug substance residual including off-specification material, non-hazardous wastes from packaging, product filter solids and chemical contaminated wastes will be disposed by on-site or off-site incineration at a permitted facility. Non-hazardous wastes that cannot be recycled or incinerated will be disposed at an off-site licensed landfill. Ash

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c) Solid Waste Controls and Citations - Drug Product Formulation (Con't)

generated from the on-site incineration process is disposed of at a permitted facility and is monitored monthly to confirm its acceptability with prevailing solid waste regulations. All solvent left from the coating solution will be recycled at an off-site permitted facility.

Solid waste disposal is regulated by the Quebec Provincial Government. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Each department supervisor is responsible for keeping MSDS of all products used in his area and having them available to all employees. The MSDSs for all products used at the site are centralized at the Health and Safety Department and through the WMIS coordinator (Work Management Information System). Each employee is trained to wear the appropriate protective equipment e.g., glasses, hair net, beard protector, long sleeves, gloves and air respiratory equipment when required.

4) West Point, Pennsylvania

a) Air Emission Controls and Citations - Drug Product Formulation

Air emissions from formulation of omeprazole may include substances identified in Appendix II. Dust produced by the drug product formulation that may be emitted to the atmosphere will be controlled by either filters or dust collectors. Emissions will be

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a) Air Emission Controls and Citations - Drug Product Formulation (Con't)

controlled to less than 0.04 grains/dscf from each stack, as required by the regulations.

For incineration of solid waste, the on-site incineration facility employs necessary operating conditions to ensure compliance with permitted emission levels. As a contingency, off-site incineration will be conducted at a permitted facility. The air emission controls for the disposal of solid waste meet requirements of the Pennsylvania Air Pollution Control Regulations under Title 25 of the Pennsylvania Code, Part I - Department of Environmental Resources Chapters 121 - 141.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new permit limits are anticipated as a result of the proposed action.

b) Liquid Waste Controls and Citations - Drug Product Formulation

The aqueous liquid emissions from the manufacturing operations will be discharged into the site wastewater collection system and will undergo pretreatment (equalization) along with other process and sanitary waste. The wastewater is discharged for further treatment to the UGTA under the limits and conditions of the UGTA contract limits. Liquid emissions resulting from the formulation of drug product will include constituents identified in Appendix II. - The equipment will be cleaned to remove residual dust from the equipment thereby minimizing the discharge of drug

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b) Liquid Waste Controls and Citations - Drug Product Formulation
(Cont)

substance to the wastewater treatment facility.

The wastewater from the West Point site is treated by the UGTA, under a permit administered by PA DER. The wastewater is subject to and in compliance with the pretreatment standards for existing sources of the Pharmaceutical Manufacturing Category under Title 40 of the Code of Federal Regulations Part 439 (Subcategory D for mixing, compounding and formulation). The wastewater is also regulated by the UGTA and in compliance with the existing contract and the, "Rules Governing the Discharge of Sanitary and Industrial Wastewaters into the Public Sewers of the Upper Gwynedd Township Authority". These regulations are based on the Federal Clean Water Act and the Pennsylvania Clean Streams Law. The current contract with the UGTA limits the daily maximum effluent flow to 2.45 million gallons per day; BOD to 250 mg/L; TSS to 300 mg/L; and pH between 5.5 - 9.0. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements and no new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Drug Product Formulation

Solid waste generated from the formulation operations include paper waste, cleaning rags, containers, gowns, and gloves. These wastes will either be incinerated on-site or as a contingency sent off-site for disposal at a permitted solid waste facility.

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c) Solid Waste Controls and Citations - Drug Product Formulation (Cont)

The waste is incinerated at permitted disposal facilities. Ash generated from the on-site incineration process is disposed of at a permitted facility and is monitored to confirm its acceptability with prevailing solid waste regulations.

Solid waste management at the West Point plant requires conformance with conditions set forth in Permits 300437, 400459, and 300501 issued by PA DER. These requirements assure comprehensive control for management of waste throughout the plant including returned market packages. The requirements of the Pennsylvania Code, Title 25, Part I - Department of Environmental Resources, Chapter 75, are the primary regulations and are subject to the requirements of the Federal Hazardous and Solid Waste Amendments, and the Pennsylvania Solid Waste Management Act.

Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. Although, the facility is not currently limited by the amount of process wastes generated, efforts will be made to minimize the amount of solid wastes generated.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available

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d) Employee Protection (Con't)

for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug product.

5) Wilson, North Carolina

a) Air Emissions Controls and Citations - Drug Product Formulation

Specific ventilation systems for packaging provide for particulate removal consisting of filtration and collection. The particulate emissions are controlled to meet the requirements of the site permit, No. 4884R9, as amended, issued by the State of North Carolina Department of Natural Resources.

The operation of the Wilson manufacturing, packaging and power generating facilities is allowed and in compliance with Air Permit Number 4884R9, as amended, issued by the North Carolina Department of Natural Resources and Community Development in accordance with Article 21B, Chapter 143, General Statutes of North Carolina and "Other Laws, Rules and Regulations". Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

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b) Liquid Emissions Controls and Citations - Drug Product Formulation

The plant wastewater is collected for metering and sampling prior to discharge to the City of Wilson collection system for processing in the Public Works Treatment Facility. The treatment facility is subject to the permit limits established by Sewer Discharge Permit Number 8406. The results from 10 years of operation indicate the multiproduct pharmaceutical facility's source control measures have satisfactorily met the discharge levels set forth in the permit.

The discharge of wastewater to the City of Wilson Wastewater Collection system is allowed under the site Sewer Connection and Discharge Permit Number 8406. The site discharge is limited to daily maximum discharges of BOD=582 lbs/day, COD=932 lbs/day, TSS=349 lbs/day, and pH 5-11. These permits are established under the city's "Rules and Regulations for the Discharge of Wastewaters into the Wastewater Treatment System of the City of Wilson, North Carolina". The City of Wilson Department of Public Works Wastewater Treatment Plant operates under National Pollutant Discharge Elimination System (NPDES) Permit Number NC0023906. No new permit limits are anticipated as a result of the proposed action.

c) Solid Waste Controls and Citations - Drug Product Formulation

All unused market packages will be sent to West Point for incineration at permitted disposal facilities. Any solid waste resulting from formulation that contains pharmaceutical residuals will be collected for disposal at an off-site incineration facility, permitted by all Federal, State and local agencies.

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c) Solid Waste Controls and Citations - Drug Product Formulation (Con't)

The Wilson plant is in compliance with the North Carolina Solid Waste and Hazardous Waste Management Rules. No new permit limits are anticipated as a result of the proposed action. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements.

d) Employee Protection

Material Safety Data Sheets are available on-site for all chemicals required by the Occupational Safety Act of 1971, the Hazards Communication Act of 1985 and Title 29 Code of Federal Regulations Part 1910.1200. Employees associated with the manufacture of drug substance have appropriate MSDSs available for their review. Employee protective clothing, such as gloves, uniforms, and safety glasses are used during the manufacturing process to assure compliance with the Occupational Safety Act of 1971 and the Hazard Communication Act of 1985 and Title 29 Code of Federal Regulations, Subpart I. Refer to Appendix IV for a copy of the MSDS for the drug substance.

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c. Effect of Application Approval on Compliance with Current Emissions Requirements

Merck & Co., Inc. states that it is in compliance with or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the bulk manufacture of omeprazole at its facility in Albany, Georgia; the formulation of omeprazole capsules at its facilities in Arecibo, Puerto Rico; Kirkland, Canada; and West Point, Pennsylvania; and the packaging of omeprazole capsules at its facilities in Arecibo, Puerto Rico and Wilson, North Carolina as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the bulk manufacture of omeprazole at its facility in Albany, Georgia; the formulation of omeprazole capsules at its facilities in Arecibo, Puerto Rico; Kirkland, Canada; and West Point, Pennsylvania; and the packaging of omeprazole capsules at its facilities in Arecibo, Puerto Rico and Wilson, North Carolina.

d. Expected Maximum Annual Production

An estimated kg/year of omeprazole will be required to supply the 5th year US market needs. Of that kg/year, approximately kg/year of omeprazole would be needed to support this GERD claim.

7. Fate of Emitted Substances to the Environment

- a. Environmentally related chemical/physical characteristics of omeprazole have been evaluated by standard analytical procedures in accordance with Good Laboratory Practices. Results are presented in detail in the technical sections of the original NDA document (Document 19-810, submitted December 21, 1988).

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Water Solubility at Ambient Room Temperature

13 mcg/ml

Acid/Base Dissociation Constants (pKa) at 25°C

The pKa values for omeprazole as determined by acid/base potentiometric titration are ~4 (pyridinium ion) and 8.8 (benzimidazole).

Distribution Constant (Partition Coefficient at Room Temperature)

The distribution coefficient K_D = concentration in organic phase/concentration in aqueous phase for the system n-octanol-water, is 240 [$\log P = 2.38$].

Melting Point/Thermal Behavior

Omeprazole melts with decomposition at ~150-155°C. On thermal analysis (DSC; Mettler TA 3000; heating rate = 2° K/min; sealed aluminum crucible) an endotherm is observed at ~150°C, which rapidly turns into an exotherm due to decomposition of the substance. The thermogram of a typical lot is shown in the figure in Appendix III.

UV Spectrum

(Please see figure in Appendix III)

In methanol, the spectrum is characterized by absorbance maxima at ~302nm.

Solution Stability

At 20°C, the half-life of omeprazole is 15 minutes or less in solutions of pH 4 and below. At pH 7, the half-life of omeprazole has been determined to be about 30 hours, and at pH 9 to be more than a week. At 25°C the half-lives were 1.9, 35, and 408 hours, at pH 5, 7, and 9 respectively. More than 50% of omeprazole was

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Solution Stability (Cont)

hydrolyzed in the pH 7 and 9 studies, before the pH of the test solutions changed by more than ± 0.05 SU.

At 37°C, the half-life of omeprazole at pH 7 has been determined to be 10 hours, and in 0.1M sodium hydroxide about one year.

Photodegradation

Photodegradation of omeprazole in an aqueous solution exposed to sunlight was studied at three different pH values. Because omeprazole was known to be susceptible to hydrolysis, the photolysis test was designed to quantify photodegradation by simultaneously monitoring hydrolytic degradation using the same three test solutions (pH 5, 7, and 9) in each test, and using dark controls at each sampling period in the photodegradation test. At pH 5, 7, and 9 exposed to sunlight, omeprazole was completely degraded within three hours, whereas for the dark controls at pH 5, 7, and 9 omeprazole was degraded to about 53, 14, and 0%, respectively within three hours. Thus, omeprazole undergoes rapid photodegradation.

Aquatic Toxicity

The 48 hour LC50 of omeprazole to *Daphnia Magna* is 88 mg/L with a 95% confidence interval of 77 and 101 mg/L, respectively. This value is considered practically non-toxic to the test organism.

b. Human Metabolism and Pharmacokinetics

Since delayed release capsules, PRIOSEC, contain an enteric-coated granule formulation of omeprazole, absorption of omeprazole occurs after granules leave the stomach. Absorption is generally rapid, however, with peak plasma levels of

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b. Human Metabolism and Pharmacokinetics (Cont)

omeprazole occurring within one to three hours. Peak plasma concentrations of omeprazole are proportional to the dose of PRIOSEC 20 mg. Delayed release capsules, PRIOSEC, are approximately 40% bioavailable.

Following single oral solution doses of omeprazole, little if any unchanged drug is excreted in urine. The majority of the dose (77%) is eliminated in urine as at least six metabolites including the sulfide, sulfone, and hydroxy metabolites. The remainder of the dose is recoverable in feces implicating a significant biliary excretion of omeprazole metabolites. The bioavailability of the oral solution is only 50 to 60%, however, indicating substantial first pass metabolism. The bioavailability of omeprazole increases as oral solution doses exceeded therapeutic levels, implying that the first pass metabolism is saturable.

The pharmacokinetics and bioavailability of omeprazole following single oral solution doses have been studied in patients with chronic hepatic disease or renal impairment. In patients with hepatic disease, 76% of the dose given by either route was recovered in urine as omeprazole metabolites. No unchanged omeprazole was recovered in urine. The plasma half-life of omeprazole in these patients was nearly three hours, and its plasma clearance average 70 mL/min. Omeprazole was 90% bioavailable.

8. Environmental Effects of Released Substances

a. Bulk Chemical Production

1. Omeprazole (MK0764)

Omeprazole is neither toxic nor inhibitory to microbial growth and degradation of other organic matter. The compound is not degraded or metabolized by a mixed microbial population. However, omeprazole is quite unstable in aqueous

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1. Omeprazole (MK0764) (Con't)

solutions. Also, the compound has a low aqueous solubility. The concentration at which toxicity is exhibited is greater than the aqueous solubility of omeprazole, thus rendering the compound non-toxic to aquatic organisms. The non-toxic nature of omeprazole, coupled with its instability and low solubility, are such that the compound will impart no adverse impact, even in the case of inadvertent entry of the drug to the aquatic environment.

2. General Chemical Operations

The environmental impact of the emitted substances from the production of bulk drug and dosage form omeprazole have been assessed through their susceptibility to biological degradation or treatment. The ratio of biological to chemical oxygen demand of the aqueous wastes emitted as a consequence of manufacturing operations suggest ease of biodegradation and substantial reduction in oxygen-demanding materials. The hydraulic and organic loadings imposed by these waste streams on existing treatment facilities are modest. At anticipated production levels, these are capable of being effectively reduced in the course of the physical-chemical and biological treatment which occurs in a well-designed and operated wastewater treatment plant. Alternative disposal methods may be considered for specific waste streams generated from the manufacturing process.

b. Dosage Form Production

The processing of the finished product involves the production of pellets and subsequent aqueous subcoating and aqueous or solvent enteric coating of the pellets which are filled into capsules. Direct introduction to the environment occurs during production from equipment cleaning, and any discharges will be primarily as solutions which are further diluted by wash water before being treated as waste. The

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b. Dosage Form Production (Con't)

quantities discharged in this manner are not expected to be significant. Small quantities of solid waste will normally be incinerated without additional consequential discharge to the air environment. The impact of these emissions is negligible.

c. Omeprazole Use

Omeprazole capsules administered to patients will enter the environment primarily in urine and feces which are significantly diluted during normal waste processing and treatment. With daily dosing of approximately 20-60 mg per patient, the total amount of drug present at any single waste treatment site would not appear to be consequential.

Also, the drug product is highly unstable hydrolytically and photolytically. Based on the physico-chemical properties of the active drug product, use is not expected to result in measurable emissions to the atmosphere or terrestrial compartment.

Omeprazole has been shown to be a drug which is well tolerated and effective in patient populations. More detailed information can be found in the supplemental NDA.

d. Omeprazole Toxicology

With the exception of patients with pathological hypersecretory conditions, omeprazole is indicated for short-term therapy only (up to four (4) weeks per treatment period in uncomplicated duodenal ulcer, up to eight (8) weeks per treatment period for uncomplicated GERD). Usage of omeprazole longer than the recommended guidelines may predispose some patients to prolonged hypergastrinemia. In rats, life long hypergastrinemia has been shown to be

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d. Omeprazole Toxicology (Cont)

associated with the sequential development of enterchromaffin-like (ECL) cell hyperplasia and gastric carcinoid tumors). The risk of prolonged hypergastrinemia in patients with duodenal ulcer or GERD is unknown. The hypergastrinemia noted during short-term courses of omeprazole 20 mg or 40 mg daily has not been shown to be associated with ECL cell hyperplasia, considered to be pre-requisite for the development of carcinoids.

In a 24-month carcinogenicity study in rats, a statistically significant ($p < 0.05$) increase in the incidence of gastric carcinoids was observed in both male and female rats. There was a marked sex difference in incidence as well as the dosage at which carcinoids were observed. In male rats, a slight increase in the incidence of carcinoids was seen at 44 mg/kg/day and greater (27.5 times the maximum recommended human dose). In female rats, carcinoid was observed at doses 1.7 mg/kg/day and greater (approximately equal to the maximum recommended human dose). The mechanisms behind the development of carcinoids have been thoroughly investigated, and the studies have established that the carcinoids are secondary to serum gastrin elevation. There was no evidence of gastric carcinoids in both male and female mice at similar doses.

Significance of these results relative to long-term treatment periods is being investigated. Patients have been treated with PRLOSEC for periods in excess of five (5) years and have not demonstrated this effect.

Several in vivo and in vitro studies with omeprazole did not detect any mutagenic properties. An Ames test using mutant strains of Salmonella species with or without microsomal activation was negative for mutagenicity. There was no evidence of

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d. Omeprazole Toxicology (Con't)

mutagenicity in an in vivo micronucleus test, in vivo chromosome aberration tests in mouse bone marrow and an in vitro mammalian cell mutation assay.

No drug-related effects on fertility were found in studies with rats.

e. Conclusion

Based on these data, no adverse environmental effects, either short or long-term, are anticipated as a consequence of the manufacture and use of the substance. This is due to low environmental levels potentially generated during production, high levels required for toxicity, and the metabolism of drug substance by patients with further breakdown during wastewater treatment. The drug product undergoes rapid photo and hydrolytic degradation.

9. Use of Resources and Energy

The raw materials utilized to manufacture the drug product and dosage form are common chemicals all of which are in ample commercial chemical supply. Energy input for bulk chemical and dosage form production is nominal and not excessive. Only very small increases in the utilization of energy is anticipated since production occurs at existing facilities. No effects upon endangered species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

10. Mitigation Measures

No potential adverse environmental impacts are foreseen from the production and use of the drug substance and product. The manufacture, distribution and use of the product

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10. Mitigation Measures (Con't)

takes place under highly regulated and controlled conditions which act to further mitigate against negative environmental consequences.

11. Alternatives to the Proposed Action

No potential adverse environmental impacts can be predicted from the drug formulation manufacture in the proposed action. Approval of this proposed action is fully supported from an environmental perspective and is preferable to non-approval.

12. List of Preparers

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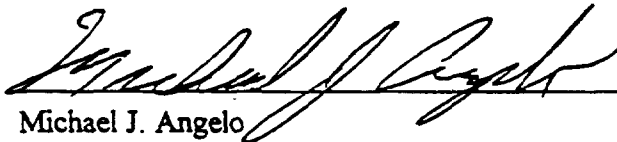
Director, Environmental Affairs

Merck Manufacturing Division

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13. Certification

The undersigned certify that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for the preparation of the environmental assessment.



Michael J. Angelo
Vice President, Safety & the Environment
Merck & Co., Inc.

8/25/95
Date

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14. References

- (1) Environmental Assessment - PRILOSEC, submitted with the approved original NDA dated December 21, 1987, is referred to as needed in the preparation of the Supplemental Environmental Assessment.

- (2) Lewis Sr. R. J., Sax, N. I., Dangerous Properties of Industrial Materials, Seventh Edition, Van Nostrand Reinhold, New York, 1989.

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APPENDICES

APPENDIX I -

APPENDIX II -

APPENDIX III -

APPENDIX IV - MATERIAL SAFETY DATA SHEET FOR DRUG SUBSTANCE

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APPENDIX IV

Omeprazole - Material Safety Data Sheets

MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Manufacturing Division - Chemical Manufacturing

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME OMEPRAZOLE DRY (MILLED) (UNMILLED) (BLENDED) PLANT MSDS CODE
FR-71

Emergency Telephone Number: (908) 594-5555

SECTION 1 - MATERIAL IDENTIFICATION

Chemical Name----- 5 Methoxy-2-[[[4-methoxy-3,5-mimethyl2-
pyridinyl) methyl]sulfinyl]-1H
benzimidazole

Label Name----- OMEPRAZOLE DRY (MILLED) (UNMILLED)
(BLENDED)

Synonyms (Common)----- Omeprazole
(Chemical)----- Not available

Material Statistical Number----- UNMILLED 2-061111; MILLED 2-061112;
BLENDED 2-061114

Material Product Number----- SP2181 (dry, milled, blended)

Chemical Classification----- Not available

Intended Use----- Pharmaceutical end product to be used
in treatment of gastric and duodenal
ulcers. Acts to inhibit production of
gastric acid.

SECTION 2 - PRINCIPAL HAZARDOUS COMPONENT(S)

<u>Component</u>	<u>Molecular Formula</u>	<u>Weight</u>	<u>CAS Number</u>	<u>Percent (%)</u>
Omeprazole	C ₁₇ H ₁₉ N ₃ O ₃ S	345.4	73590-58-6	ca 100

SECTION 3 - PHYSICAL PROPERTY DATA

Appearance----- White crystalline solid

Odor Threshold Level (ppm)----- Not available

Boiling Point (°C/°F)----- Not applicable

Freezing Point (°C/°F)----- Not applicable

Melting Point (°C/°F)----- 156°C/313°F

pH ----- Not available

*** Continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Manufacturing Division - Chemical Manufacturing

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME OMEPRAZOLE DRY (MILLED) (UNMILLED) (BLENDED)

PLANT MSDS CODE
FR-71

Emergency Telephone Number: (908) 594-5555

Solubility in water----- Slightly: 1.13 mg/ml

Specific Gravity (Water = 1)----- Not applicable

Vapor Density (Air=1)----- Not applicable

Vapor Pressure (mm Hg @ °C/°F)--- Not applicable

Volatile Components (% w/w)----- None

SECTION 4 - FIRE AND EXPLOSION HAZARD DATA

Flash Point (°C/°F)----- Not applicable

Flash Point Test Method----- Not applicable

Autoignition Temperature (°C/°F)- Not available

Flammable Limits -LEL (%)----- Not applicable

-UEL (%)----- Not applicable

Combustibility Information----- Not available

Dust Explosivity Information----- Omeprazole can form explosive mixtures
in air. The maximum developed pressure
in an unvented 20 liter test vessel was
117 psig.

Shock Sensitivity Information---- Not available

Extinguishing Media----- Small fires: Use dry chemical, carbon
dioxide, halon, water spray, or alcohol
foam.

Large fires: Use water spray, fog or
alcohol foam.

Special Fire Fighting Procedures- Wear positive pressure self-contained
breathing apparatus (SCBA) and full
turnout gear.

Fire/Explosion Hazards----- Omeprazole powder is combustible and
can form explosive mixtures with air.

*** Continued on next page ***

MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
 Merck Manufacturing Division - Chemical Manufacturing

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME OMEPRAZOLE DRY (MILLED) (UNMILLED) (BLENDED) PLANT MSDS CODE
 FR-71

Emergency Telephone Number: (908) 594-5555

Decomposition Products

Resulting From A Fire----- Fire will produce toxic gases including but not necessarily limited to SO₂, NO_x, CO, CO₂, formaldehyde, formic acid, and other complex decomposition products in smoke.

SECTION 5 - REACTIVITY DATA

Stability (Normal Storage Conditions)-- Stable under normal cool, dry conditions at normal pressure.

Storage Conditions to Avoid----- Bulk material may be ignited by heat of fire. Dust may be ignited by heat, flames, or spark.

Thermal Stability/Instability Information- Stable under normal conditions.

Incompatibilities (Chemical Entities)- Unknown.

Incompatibilities (Materials of Construction)- Unknown.

Hazardous Polymerizations----- None known

SECTION 6 - EMERGENCY AND FIRST AID PROCEDURES

Eye Contact----- Flush copiously with water for 15 minutes. Get medical attention.

Skin Contact----- Remove contaminated clothing and shoes. Wash affected areas with soap and water until no trace of chemical remains. If irritation develops get medical treatment.

Inhalation----- Remove victim to fresh air. No emergency medical treatment is needed.

Ingestion----- Not acutely toxic. Seek immediate medical treatment.

*** Continued on next page ***

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Merck Chemical Manufacturing Division

MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Manufacturing Division - Chemical Manufacturing

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME OMEPRAZOLE DRY (MILLED) (UNMILLED) (BLENDED) PLANT MSDS CODE
FR-71
Emergency Telephone Number: (908) 594-5555

Notes to Physician----- Omeprazole is a gastric acid secretion inhibitor which degrades in acid environments such as the stomach. The therapeutic dose is 20 to 60 mg/day. The pharmacological effect (inhibition of gastric acid secretion) is reversible after five days.

SECTION 7 - HEALTH HAZARD DATA

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
Omeprazole	Not established	Not established	0.5 mg/m ³

Carcinogen Designation----- None known.

Effects of Acute Exposure

Eye Contact----- May cause mild irritation.

Skin Contact----- Omeprazole may cause contact skin irritation and sensitization. Omeprazole has produced evidence of delayed contact hypersensitivity in the guinea pig maximization test.

Inhalation----- Inhaled material will be partly absorbed in the lungs and may produce the pharmacologic effect if absorbed in sufficient quantity (greater than 5 milligrams per day dose). Any material evacuated from the lungs and swallowed will be degraded by acid in the stomach. Inhalation may produce allergic respiratory symptoms.

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Ingestion----- Non-toxic orally. A no-observable-effect dose level of 5 mg/day has been established for gastric acid inhibition. In animal studies the compound is essentially non-toxic by the oral route. The compound is degraded in acid pH and hence will be degraded in the stomach acid.

Effects of Chronic Exposure----- Omeprazole has shown no evidence of mutagenicity or genotoxicity in a series of invitro and invivo tests. Reproductive studies have not revealed any evidence of adverse effects on reproduction at doses up to 138 mg/kg. Chronic toxicity studies found no evidence of carcinogenicity in mice orally administered 70 or 140 mg/kg/day for 66 weeks. Rats given the same dose, however, developed gastric ECL cell carcinoids. The biological half-life of omeprazole in blood plasma is 0.5 to 1 hour. The pharmacological effect (suppressed gastric acid production) is reversible within 5 days.

Quantitative Toxicity Data

OMEPRAZOLE

LD50 ORAL MOUSE ----- Greater than 4,000 mg/kg
LD50 ORAL RAT ----- Greater than 4,000 mg/kg
LD50 INTRAVENOUS MOUSE --- 83 mg/kg
LD50 INTRAVENOUS RAT ----- Greater than 50 mg/kg

SECTION 8 -SPILL/LEAK/DISPOSAL PROCEDURE

Steps to be taken in case materials released:

Contact emergency response personnel.
Keep unnecessary persons away. If emergency response personnel are unavailable, vacuum, shovel, or sweep

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up spilled material and place in an appropriate container for disposal. Use suitable protective equipment (Section 9). Follow all fire prevention procedures (Section 4).

For additional assistance, CHEMTREC provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents:
TELEPHONE CHEMTREC AT 1-800-424-9300.

Environmental Data----- LC50 (Daphnia magna): 88.00 ppm

Waste Disposal Information----- Avoid contact of spilled materials and run-off with soil and surface waterways. Dispose of or treat all spill residues including contaminated soils following all federal, state, and local regulations.

SECTION 9 - SPECIAL PROTECTION INFORMATION

Respiratory----- Use toxic dust respirator or full-face continuous air supplied respirator (supplied air or self contained breathing apparatus) when handling material.

Hands/Arms----- Wear butyl or neoprene rubber gloves and vinyl apron for normal handling. In spill situation, additionally wear Tyvek suit or similar protective disposable garment.

Eye/Face----- Wear chemical goggles if handling exposed material.

Ventilation----- Local exhaust ventilation should be used to capture dry omeprazole dust at the point of generation.

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MERCK & CO., INC., P.O. BOX 2000, RARITON, N.J. 07065
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 FR-71
 Emergency Telephone Number: (908) 594-5555

SECTION 10 - SPECIAL PRECAUTIONS

Special Precautions to be taken when:

- Handling----- Wear personal protective equipment and clothing described in Section 9.
- Storing----- Store at or below 46°F (8°C) for milled and blended and at or below 32°F (0°C) for unmilled in a dry well ventilated place. Keep containers tightly closed and stored away from incompatible materials.
- Other----- None

SECTION 11 - BASIC TRANSPORTATION DESCRIPTION

- U.S. DOT----- Not available
- ICAO/IATA----- Not available
- IMO----- Not available
- Hazardous Substance-Reportable Quantity (RQ)--- Not available

SECTION 12 - INTER-PLANT COMMUNICATION

List all other MMD plants requiring a copy of this MSDS---None

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MERCK & CO., INC., P.O. BOX 2000, RAHWAY, N.J. 07065
Merck Manufacturing Division - Chemical Manufacturing

***** MATERIAL SAFETY DATA SHEET *****

LABEL NAME OMEPRAZOLE DRY (MILLED) (UNMILLED) (BLENDED)

PLANT MSDS CODE
FR-71

Emergency Telephone Number: (908) 594-5555

SECTION 13 - MSDS PREPARATION (REVISION 1)

B. F. Bastian

MCMD/Site Safety-----Date: July 25, 1990

L. D. Forshey

Technical Operations-----Date: July 31, 1990

M. D. Slaymaker

Environmental Control-----Date: August 9, 1990

M. Babos

Corporate Environmental Resources-----Date: September 19, 1990

R. Cutro

Technical Operations Administration-----Date: August 23, 1990

E. Sargent, Ph.D.

Corporate Safety & Industrial Hygiene-----Date: August 29, 1990

SECTION 14 - MERCK DISCLAIMER

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO., INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

MAY - 9 1995

NDA 19-810/S-036

Astra Merck
Attention: Eileen M. Leonard, M.D.
725 Chesterbrook Blvd.
Wayne, Pennsylvania 19087-5677

Dear Dr. Leonard:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Prilosec (omeprazole) Delayed-Release Capsules

NDA Number: 19-810

Supplement Number: S-036

Therapeutic Classification: Standard

Date of Supplement: May 4, 1995

Date of Receipt: May 5, 1995

This supplement provides for a new indication: treatment of gastroesophageal reflux disease (GERD).

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)(1) of the Act on July 4, 1995 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal
and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM #6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Maria R. Walsh
Consumer Safety Officer
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research