# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# NDA 19-810/S-003 & S-058

***Trade Name:*** Prilosec Delayed Release Tablets

***Generic Name:*** omeprazole

***Sponsor:*** AstraZeneca LP

***Approval Date:*** February 24, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-810/S003 & S058

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-810/S-003 & S-058

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-003
NDA 19-810/S-058

AstraZeneca LP
Attention: Nicholas J. Troise
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

Please refer to your supplemental new drug application, NDA 19-810/S-058, dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

We also refer to your supplemental new drug application, NDA 19-810/003, dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 22, 2003, received on December 23, 2003. Your submissions constituted a complete response to our October 3, 2003 action letter.

Supplemental new drug application, NDA 19-810/S-058, proposes revisions to the package insert under the ***Carcinogenicity, Mutagenicity, Impairment of Fertility/, Pregnancy/,*** **and** ***Nursing Mothers*** subsections of the **PRECAUTIONS** section.

Supplemental new drug application, NDA 19-810/003, proposes revisions to the package insert under the ***Carcinogenicity, Mutagenicity, Impairment of Fertility*** subsection of the **PRECAUTIONS** section, regarding a primary malignant tumor observed in a single rat.

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on December 22, 2003.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 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, call Monika Houstoun, Regulatory Project Manager, at (301) 827-9333.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Labeling

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

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/s/

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Joyce Korvick
2/23/04 04:23:23 PM
for Dr. Robert Justice

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-810/S-003 & S058

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-058 and S-003

Astra-Zeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087

Dear Dr. Horowitz:

Please refer to your supplemental new drug application (S-058) dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 24, 1999, October 7, 1999, August 4, 2000, January 31, 2001, August 16, 2001, July 31, 2002, and August 16, 2002. Your submission of July 31, 2002 constituted a complete response to our February 14, 2002 action letter.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers*, including a change in the *Pregnancy Category* from *C* to *B*.

We also refer to your supplemental new drug application (S-003) dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated April 6, 1990, May 1, 1990, March 24, 1995, February 5, 2001, July 31, 2002 and August 16, 2002. Your submission of July 31, 2002 constituted a complete response to our February 14, 2002 action letter.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility* regarding a primary malignant tumor observed in a single rat.

We completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert. In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of these supplemental applications.

If you have any questions, call Melissa Hancock Furness, Regulatory Project Manager, at (301)-827-7450.

Sincerely,

{See appended electronic signature page}

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

Enclosure

23 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/
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Joyce Korvick
1/31/03 10:37:26 AM
for Dr. Robert Justice

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-058 and S-003

Astra-Zeneca LP
Attention: Michael Angioli
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Angioli:

Please refer to your supplemental new drug application (S-058) dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 24, 1999, October 7, 1999, August 4, 2000, January 31, 2001, August 16, 2001, July 31, 2002, and August 16, 2002. Your submission of April 3, 2003 constituted a complete response to our January 31, 2003 action letter.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers*, including a change in the *Pregnancy Category* from *C* to *B*.

We also refer to your supplemental new drug application (S-003) dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec® (omeprazole) Delayed-Release Capsules.

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This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility* regarding a primary malignant tumor observed in a single rat.

We completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling text for the package insert. In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

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Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of these supplemental applications.

If you have any questions, call Melissa Hancock Furness, Regulatory Project Manager, at (301)-827-7450.

Sincerely,

{See appended electronic signature page}

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

Enclosure

23 Page(s) Withheld

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

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Joyce Korvick
10/3/03 12:52:53 PM
for Dr. Robert Justice

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-810/S-058
NDA 19-810/S-003

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your supplemental new drug application (S-058) dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 24, 1999, October 7, 1999, August 4, 2000, January 31, 2001, and August 16, 2001. Your submission of August 16, 2001 constituted a complete response to our February 7, 2001 action letter.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers*, including a change in the *Pregnancy Category* from *C* to *B*.

We also refer to your supplemental new drug application (S-003) dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated April 6, 1990, May 1, 1990, March 24, 1995, and February 5, 2001. Your submission of February 5, 2001 constituted a complete response to our July 1, 1997 action letter.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility* regarding a primary malignant tumor observed in a single rat.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

**PRECAUTIONS**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

of treatment related brain astrocytoma in a 52-week toxicity study in Sprague-Dawley rats for the following reasons.

1. The brain astrocytomas have been observed in treated groups only but not in the concurrent controls.

2. Historically in this strain of rat, there is no background incidence in one-year toxicity studies.

3. Negative findings in the mouse tests have no bearing on the findings in the rat toxicology study.

4. In the two-year carcinogenicity study in rats, 50 animals/group is a small sample and a negative finding in such a study does not eliminate the positive findings in a study of shorter duration.

5. A gastric adenocarcinoma occurred in a second rat carcinogenicity study of omeprazole in which animals were treated for only one year while such tumors were not observed in animals treated for two years. This finding was included in the labeling with a qualifying statement.

6. Inclusion of tumorigenic findings in toxicology studies under this section of the labeling are included in the package inserts of other proton pump inhihitors.

You may wish to add a qualifying statement about the findings of the 52-week toxicity study in rats.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D.
Deputy Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
2/14/02 03:26:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-810/S-058

FEB 7, 2001

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailcode: E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your supplemental new drug application dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated September 24, 1999, October 7, 1999, August 4, 2000, and January 31, 2001. Your submission of August 4, 2000 constituted a complete response to our October 7, 1999 action letter.

This supplemental application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility; Pregnancy;* and *Nursing Mothers*, including a change in the *Pregnancy Category* from *C* to *B*.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. [redacted] was seen in one rat (2%). In a 52-week toxicity study in [redacted]

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

**Pregnancy**
**Omeprazole**
*Pregnancy Category C*

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used [redacted] justifies the potential risk to the fetus.

**Nursing Mothers**
Omeprazole concentrations have been measured in breast milk of a woman following oral

administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This [redacted] would correspond to 0.004 mg of omeprazole in 200 ml of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

*{See appended electronic signature page}*

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/
---
Lilia Talarico
2/7/01 03:27:45 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**19-810/S003 & S058**

# NON-APPROVABLE LETTER

WALSH

NDA 19-810/S-058

OCT 7 1999

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your supplemental new drug application dated October 7, 1998, received October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

We also refer to your submission dated September 24, 1999. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This supplement proposes the following changes: Revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers.* These revisions include a change in the *Pregnancy Category* from *C* to *B*.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

> The epidemiological data submitted do not provide adequate information to evaluate the fetal risk from omeprazole exposure during pregnancy.

A large, prospective cohort study in women of child-bearing potential receiving omeprazole for gastroesophageal reflux disease (GERD) and who become pregnant while receiving omeprazole may provide useful information. The feasibility and design characteristics of such a study can be discussed at a future meeting between representatives of your firm and the FDA.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

LT 10-7-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research .

cc:
Archival NDA 19-810/S-058
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/S.Aurecchia
H.Gallo-Torres
K.Robie-Suh
J.Choudary

Drafted by: M.Walsh 10/7/99
Initialed by: S.Aurecchia 10/7/99
L.Talarico 10/7/99
final: M.Walsh 10/7/99
filename: 19810S58.NA.doc

NOT APPROVABLE (NA)

6 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*
**19810 S003 & S058**

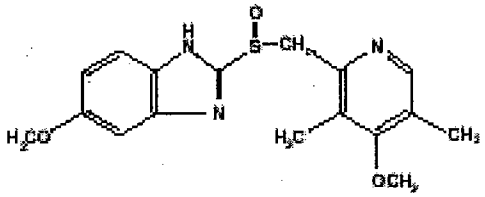
# LABELING

9194140
640004-40

# PRILOSEC®
*(OMEPRAZOLE)*
DELAYED-RELEASE CAPSULES

## DESCRIPTION

The active ingredient in PRILOSEC (omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

PRILOSEC is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10 mg, 20 mg or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hypromellose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin-NF, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C Blue #2, D&C Red #7 Calcium Lake, and, in addition, the 10 mg and 40 mg capsule shells also contain D&C Yellow #10.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics and Metabolism: Omeprazole

PRILOSEC Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately 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 intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%.

The bioavailability of omeprazole increases slightly upon repeated administration of PRILOSEC Delayed-Release Capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 $m^2$, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

PRILOSEC Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, PRILOSEC Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in $C_{max}$ was observed without a significant change in AUC for PRILOSEC Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

The pharmacokinetics of omeprazole have been investigated in pediatric patients of different ages.

Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared to Adults

| Single or Repeated Oral Dosing | Children† < 20 kg | Children† > 20 kg | Adults‡ (mean 76 kg) |
|---|---|---|---|

| /Parameter | 2-5 years 10 mg | 6-16 years 20 mg | 23-29 years (n=12) |
|---|---|---|---|
| | Single Dosing | | |
| $C_{max}$* (ng/mL) | 288 (n=10) | 495 (n=49) | 668 |
| AUC* (ng h/mL) | 511 (n=7) | 1140 (n=32) | 1220 |
| | Repeated Dosing | | |
| $C_{max}$* (ng/mL) | 539 (n=4) | 851 (n=32) | 1458 |
| AUC* (ng h/mL) | 1179 (n=2) | 2276 (n=23) | 3352 |

Note: * = plasma concentration adjusted to an oral dose of 1 mg/kg.
†Data from single and repeated dose studies
‡Data from a single and repeated dose study
Doses of 10, 20 and 40 mg Omeprazole as Enteric-Coated Granules

Following comparable mg/kg doses of omeprazole, younger children (2-5 years) have lower AUCs than children 6 – 16 years or adults; AUCs of the latter two groups did not differ. (See DOSAGE AND ADMINISTRATION – Pediatric Patients.)

## Pharmacokinetics: Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased ($C_{max}$, $AUC_{0-24}$, and $T_{1/2}$ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean $C_{max}$ was 10% greater, the mean $C_{min}$ was 27% greater, and the mean $AUC_{0-8}$ was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean $C_{max}$ was 45% greater, the mean $C_{min}$ was 57% greater, and the mean $AUC_{0-8}$ was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

Clarithromycin Tissue Concentrations
2 hours after Dose[1]

| Tissue | Clarithromycin | Clarithromycin + Omeprazole |
|---|---|---|
| Antrum | 10.48 ± 2.01 (n = 5) | 19.96 ± 4.71 (n = 5) |
| Fundus | 20.81 ± 7.64 (n = 5) | 24.25 ± 6.37 (n = 5) |
| Mucus | 4.15 ± 7.74 (n = 4) | 39.29 ± 32.79 (n = 4) |

[1] Mean ± SD (µg/g)

For information on clarithromycin pharmacokinetics and microbiology, consult the clarithromycin package insert, CLINICAL PHARMACOLOGY section.

The pharmacokinetics of omeprazole, clarithromycin, and amoxicillin have not been adequately studied when all three drugs are administered concomitantly.

For information on amoxicillin pharmacokinetics and microbiology, see the amoxicillin package insert, ACTIONS, PHARMACOLOGY and MICROBIOLOGY sections.

## Pharmacodynamics

### *Mechanism of Action*

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or $H_2$ histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the $H^+/K^+$ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it 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. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

### *Antisecretory Activity*

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal $H^+/K^+$ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2-6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies
of the Mean Antisecretory Effects of Omeprazole
After Multiple Daily Dosing

| Parameter | Omeprazole 20 mg | | Omeprazole 40 mg | |
|---|---|---|---|---|
| % Decrease in | Max | Min | Max | Min |
| Basal Acid Output | 78* | 58-80 | 94* | 80-93 |
| % Decrease in Peak Acid Output | 79* | 50-59 | 88* | 62-68 |
| % Decrease in 24-hr. Intragastric Acidity | | 80-97 | | 92-94 |

* Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

### *Enterochromaffin-like (ECL) Cell Effects*

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of $H_2$-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.)

However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

*Serum Gastrin Effects*

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine $H_2$-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

*Other Effects*

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of PRILOSEC 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

## Clinical Studies

*Duodenal Ulcer Disease*

*Active Duodenal Ulcer*— In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

| | PRILOSEC 20 mg a.m. (n = 99) | Placebo a.m. (n = 48) |
|---|---|---|
| Week 2 | *41 | 13 |
| Week 4 | *75 | 27 |

*($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with PRILOSEC 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received PRILOSEC had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with PRILOSEC 20 mg once a day than with ranitidine 150 mg b.i.d. ($p < 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

| | PRILOSEC 20 mg a.m. (n = 145) | Ranitidine 150 mg b.i.d. (n = 148) |
|---|---|---|
| Week 2 | 42 | 34 |
| Week 4 | *82 | 63 |

*($p < 0.01$)

Healing occurred significantly faster in patients treated with PRILOSEC than in those treated with ranitidine 150 mg b.i.d. ($p < 0.01$).

In a foreign multinational randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of PRILOSEC were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of PRILOSEC were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of PRILOSEC, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

| | PRILOSEC 20 mg (n = 34) | PRILOSEC 40 mg (n = 36) | Ranitidine 150 mg b.i.d. (n = 35) |
|---|---|---|---|
| Week 2 | * 83 | * 83 | 53 |
| Week 4 | * 97 | *100 | 82 |
| Week 8 | 100 | 100 | 94 |

*($p \leq 0.01$)

*H. pylori Eradication in Patients with Duodenal Ulcer Disease*

*Triple Therapy(PRILOSEC/clarithromycin/amoxicillin)*— Three U.S., randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (n = 558) compared PRILOSEC plus clarithromycin plus amoxicillin to clarithromycin plus amoxicillin. Two studies (126 and 127) were conducted in patients with an active duodenal ulcer, and the other study (M96-446) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. The dose regimen in the studies was PRILOSEC 20 mg b.i.d. plus clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days; or clarithromycin 500 mg b.i.d. plus amoxicillin 1 g b.i.d. for 10 days. In studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of PRILOSEC 20 mg q.d. Endpoints studied were

eradication of *H. pylori* and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest®, histology and culture in all three studies. For a given patient, *H. pylori* was considered eradicated if at least two of these tests were negative, and none was positive.

The combination of omeprazole plus clarithromycin plus amoxicillin was effective in eradicating *H. pylori.*

Per-Protocol and Intent-to-Treat *H. pylori* Eradication Rates
% of Patients Cured [95% Confidence Interval]

| | PRILOSEC +clarithromycin +amoxicillin | | Clarithromycin +amoxicillin | |
|---|---|---|---|---|
| | Per-Protocol † | Intent-to-Treat ‡ | Per-Protocol † | Intent-to-Treat ‡ |
| Study 126 | ·77 [64, 86] (n = 64) | ·69 [57, 79] (n = 80) | 43 [31, 56] (n = 67) | 37 [27, 48] (n = 84) |
| Study 127 | ·78 [67, 88] (n = 65) | ·73 [61, 82] (n = 77) | 41 [29, 54] (n = 68) | 36 [26, 47] (n = 83) |
| Study M96-446 | ·90 [80, 96] (n = 69) | ·83 [74, 91] (n = 84) | 33 [24, 44] (n = 93) | 32 [23, 42] (n = 99) |

† Patients were included in the analysis if they had confirmed duodenal ulcer disease (active ulcer, studies 126 and 127; history of ulcer within 5 years, study M96-446) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest®, histology, and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. The impact of eradication on ulcer recurrence has not been assessed in patients with a past history of ulcer.

‡ Patients were included in the analysis if they had documented *H. pylori* infection at baseline and had confirmed duodenal ulcer disease. All dropouts were included as failures of therapy.

· ($p < 0.05$) versus clarithromycin plus amoxicillin.

*Dual Therapy (PRILOSEC/clarithromycin)*— Four randomized, double-blind, multicenter studies (M93-067, M93-100, M92-812b, and M93-058) evaluated PRILOSEC 40 mg q.d. plus clarithromycin 500 mg t.i.d. for 14 days, followed by PRILOSEC 20 mg q.d. (M93-067, M93-100, M93-058) or by PRILOSEC 40 mg q.d. (M92-812b) for an additional 14 days in patients with active duodenal ulcer associated with *H. pylori*. Studies M93-067 and M93-100 were conducted in the U.S. and Canada and enrolled 242 and 256 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 219 patients in Study M93-067 and 228 patients in Study M93-100. These studies compared the combination regimen to PRILOSEC and clarithromycin monotherapies. Studies M92-812b and M93-058 were conducted in Europe and enrolled 154 and 215 patients, respectively. *H. pylori* infection and duodenal ulcer were confirmed in 148 patients in study M92-812b and 208 patients in Study M93-058. These studies compared the combination regimen to omeprazole monotherapy. The results for the efficacy analyses for these studies are described below. *H. pylori* eradication was defined as no positive test (culture or histology) at 4 weeks following the end of treatment, and two negative tests were required to be considered eradicated of *H. pylori.* In the per-protocol analysis, the following patients were excluded: dropouts, patients with missing *H. pylori* tests post-treatment, and patients that were not assessed for *H. pylori* eradication because they were found to have an ulcer at the end of treatment.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori.*

*H. pylori* Eradication Rates (Per-Protocol Analysis at 4 to 6 Weeks)
% of Patients Cured [95% Confidence Interval]

| | PRILOSEC + Clarithromycin | PRILOSEC | Clarithromycin |
|---|---|---|---|
| **U.S. Studies** | | | |
| Study M93-067 | 74 [60, 85]†‡ (n = 53) | 0 [0, 7] (n = 54) | 31 [18, 47] (n = 42) |
| Study M93-100 | 64 [51, 76]†‡ (n = 61) | 0 [0, 6] (n = 59) | 39 [24, 55] (n = 44) |
| **Non U.S. Studies** | | | |
| Study M92-812b | 83 [71, 92] ‡ (n = 60) | 1 [0, 7] (n = 74) | N/A |
| Study M93-058 | 74 [64, 83] ‡ (n = 86) | 1 [0, 6] (n = 90) | N/A |

† Statistically significantly higher than clarithromycin monotherapy ($p < 0.05$)
‡ Statistically significantly higher than omeprazole monotherapy ($p < 0.05$)

Ulcer healing was not significantly different when clarithromycin was added to omeprazole therapy compared to omeprazole therapy alone.

The combination of omeprazole and clarithromycin was effective in eradicating *H. pylori* and reduced duodenal ulcer recurrence.

Duodenal Ulcer Recurrence Rates by
*H. pylori* Eradication Status
% of Patients with Ulcer Recurrence

| | *H. pylori* eradicated# | *H. pylori* not eradicated# |
|---|---|---|
| **U.S. Studies** † | | |
| 6 months post-treatment | | |
| Study M93-067 | *35 (n = 49) | 60 (n = 88) |
| Study M93-100 | *8 (n = 53) | 60 (n = 106) |
| **Non U.S. Studies** ‡ | | |
| 6 months post-treatment | | |
| Study M92-812b | *5 (n = 43) | 46 (n = 78) |
| Study M93-058 | *6 (n = 53) | 43 (n = 107) |
| 12 months post-treatment | | |
| Study M92-812b | *5 (n = 39) | 68 (n = 71) |

# *H. pylori* eradication status assessed at same timepoint as ulcer recurrence
† Combined results for PRILOSEC + clarithromycin, PRILOSEC, and clarithromycin treatment arms
‡ Combined results for PRILOSEC + clarithromycin and PRILOSEC treatment arms
* ($p \leq 0.01$) versus proportion with duodenal ulcer recurrence who were not *H. pylori* eradicated

## *Gastric Ulcer*

In a U.S. multicenter, double-blind, study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

| | PRILOSEC 20 mg q.d. (n = 202) | PRILOSEC 40 mg q.d. (n = 214) | Placebo (n = 104) |
|---|---|---|---|
| Week 4 | 47.5** | 55.6** | 30.8 |
| Week 8 | 74.8** | 82.7**,* | 48.1 |

** ($p < 0.01$) PRILOSEC 40 mg or 20 mg versus placebo
* ($p < 0.05$) PRILOSEC 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

| | PRILOSEC 20 mg q.d. (n = 200) | PRILOSEC 40 mg q.d. (n = 187) | Ranitidine 150 mg b.i.d. (n = 199) |
|---|---|---|---|
| Week 4 | 63.5 | 78.1**,++ | 56.3 |
| Week 8 | 81.5 | 91.4**,++ | 78.4 |

** ($p < 0.01$) PRILOSEC 40 mg versus ranitidine
++ ($p < 0.01$) PRILOSEC 40 mg versus 20 mg

## *Gastroesophageal Reflux Disease (GERD)*
### *Symptomatic GERD*

A placebo controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[a]

| | PRILOSEC 20 mg a.m. | PRILOSEC 10 mg a.m. | Placebo a.m. |
|---|---|---|---|
| All patients | 46*,† (n = 205) | 31† (n = 199) | 13 (n = 105) |
| Patients with confirmed GERD | 56*,† (n = 115) | 36† (n = 109) | 14 (n = 59) |

[a]Defined as complete resolution of heartburn
*($p < 0.005$) versus 10 mg
†($p < 0.005$) versus placebo

### *Erosive Esophagitis*

In a U.S. multicenter double-blind placebo controlled study of 20 mg or 40 mg of PRILOSEC Delayed-Release Capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

| Week | 20 mg PRILOSEC (n = 83) | 40 mg PRILOSEC (n = 87) | Placebo (n = 43) |
|---|---|---|---|
| 4 | 39** | 45** | 7 |
| 8 | 74** | 75** | 14 |

** ($p < 0.01$) PRILOSEC versus placebo.

In this study, the 40 mg dose was not superior to the 20 mg dose of PRILOSEC in the percentage healing rate. Other controlled clinical trials have also shown that PRILOSEC is effective in severe GERD. In comparisons with histamine $H_2$-receptor antagonists in patients with erosive esophagitis, grade 2 or above, PRILOSEC in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with PRILOSEC than in those taking placebo or histamine $H_2$- receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

### *Long Term Maintenance Treatment of Erosive Esophagitis*

In a U.S. double-blind, randomized, multicenter, placebo controlled study, two dose regimens of PRILOSEC were studied in patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

Life Table Analysis

| | PRILOSEC 20 mg q.d. (n = 138) | PRILOSEC 20 mg 3 days per week (n = 137) | Placebo (n = 131) |
|---|---|---|---|
| Percent in endoscopic remission at 6 months | *70 | 34 | 11 |

*(p < 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 20 mg 3 consecutive days per week or placebo.

In an international multicenter double-blind study, PRILOSEC 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

Life Table Analysis

| | PRILOSEC 20 mg q.d. (n = 131) | PRILOSEC 10 mg q.d. (n = 133) | Ranitidine 150 mg b.i.d. (n = 128) |
|---|---|---|---|
| Percent in endoscopic remission at 12 months | *77 | ‡58 | 46 |

* (p = 0.01) PRILOSEC 20 mg q.d. versus PRILOSEC 10 mg q.d. or Ranitidine.
‡ (p = 0.03) PRILOSEC 10 mg q.d. versus Ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing 20 mg daily of PRILOSEC was effective, while 10 mg did not demonstrate effectiveness.

### *Pathological Hypersecretory Conditions*

In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, PRILOSEC Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see DOSAGE AND ADMINISTRATION). PRILOSEC was well tolerated at these high dose levels for prolonged periods (> 5 years in some patients). In most ZE patients, serum gastrin levels were not modified by PRILOSEC. However, in some patients serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with PRILOSEC developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of PRILOSEC. (See ADVERSE REACTIONS.)

## Microbiology

Omeprazole and clarithromycin dual therapy and omeprazole, clarithromycin and amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

*Helicobacter*
*Helicobacter pylori*

**Pretreatment Resistance**

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446).

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest®.

**Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

| Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes [a] | | | | | | |
|---|---|---|---|---|---|---|
| Clarithromycin Pretreatment Results | | Clarithromycin Post-treatment Results | | | | |
| | | *H. pylori* negative - eradicated | *H. pylori* positive - not eradicated | | | |
| | | | Post-treatment susceptibility results | | | |
| | | | S [b] | I [b] | R [b] | No MIC |
| Dual Therapy - (omeprazole 40 mg q.d./clarithromycin 500 mg t.i.d. for 14 days followed by omeprazole 20 mg q.d. for another 14 days) (Studies M93-067, M93-100) | | | | | | |
| Susceptible [b] | 108 | 72 | 1 | | 26 | 9 |
| Intermediate [b] | 1 | | | | 1 | |
| Resistant [b] | 4 | | | | 4 | |
| Triple Therapy - (omeprazole 20 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d. for 10 days - Studies 126, 127, M96-446; followed by omeprazole 20 mg q.d. for another 18 days - Studies 126, 127) | | | | | | |
| Susceptible [b] | 171 | 153 | 7 | | 3 | 8 |
| Intermediate [b] | | | | | | |
| Resistant [b] | 14 | 4 | 1 | | 6 | 3 |

[a] Includes only patients with pretreatment clarithromycin susceptibility test results
[b] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy or omeprazole/clarithromycin dual therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

**Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

**Susceptibility Test for *Helicobacter pylori***

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs[1]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7$ - $1 \times 10^8$ CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar

plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

| Clarithromycin MIC (µg/mL)[a] | Interpretation |
|---|---|
| ≤ 0.25 | Susceptible (S) |
| 0.5 | Intermediate (I) |
| ≥ 1.0 | Resistant (R) |

| Amoxicillin MIC (µg/mL)[a,b] | Interpretation |
|---|---|
| ≤ 0.25 | Susceptible (S) |

[a] These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

| Microorganism | Antimicrobial Agent | MIC (µg/mL)[a] |
|---|---|---|
| *H. pylori* ATCC 43504 | Clarithromycin | 0.016- 0.12 (µg/mL) |
| *H. pylori* ATCC 43504 | Amoxicillin | 0.016- 0.12 (µg/mL) |

[a]These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

## INDICATIONS AND USAGE

### Duodenal Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori*.

PRILOSEC Delayed-Release Capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY, Clinical Studies and DOSAGE AND ADMINISTRATION).

Among patients who fail therapy, PRILOSEC with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

### Gastric Ulcer

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

### Treatment of Gastroesophageal Reflux Disease (GERD)

*Symptomatic GERD*

PRILOSEC Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

*Erosive Esophagitis*

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.)

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

### Maintenance of Healing of Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

### Pathological Hypersecretory Conditions

PRILOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

## CONTRAINDICATIONS

### Omeprazole

PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

### Clarithromycin

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.)

### Amoxicillin

Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

## WARNINGS

### Clarithromycin

**CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)**

### Amoxicillin

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.** (See WARNINGS in prescribing information for amoxicillin.)

### Antimicrobials

**Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** (See WARNINGS in prescribing information for clarithromycin and amoxicillin.)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

## PRECAUTIONS

### General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

## Information for Patients

PRILOSEC Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

## Drug Interactions

*Other*

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of PRILOSEC.

*Combination Therapy with Clarithromycin*

Co-administration of omeprazole and clarithromycin have resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended. (See also CONTRAINDICATIONS, Clarithromycin, above. Please refer to full prescribing information for clarithromycin before prescribing.)

## Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

## Pregnancy

### Omeprazole

*Pregnancy Category C*

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[2]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[3] *In utero* exposure to omeprazole was not associated with increased risk of any

malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[4] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[5] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

### Clarithromycin

*Pregnancy Category C.* See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

### Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL

of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

The safety and effectiveness of PRILOSEC have been established in the age group 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The safety and effectiveness of PRILOSEC have not been established for pediatric patients less than 2 years of age. Use of PRILOSEC in the age group 2 years to 16 years is supported by evidence from adequate and well-controlled studies of PRILOSEC in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism: Omeprazole).

*Treatment of Gastroesophageal Reflux Disease (GERD)*

Symptomatic GERD

In an uncontrolled, open-label study of patients aged 2 years to 16 years with a history of symptoms suggestive of nonerosive GERD, 113 patients were assigned to receive a single daily dose of omeprazole (10 mg or 20 mg, based on body weight) either as an intact capsule or as an open capsule in applesauce. Results showed success rates of 60% (10 mg omeprazole) and 59% (20 mg omeprazole) in reducing the number and intensity of either pain-related symptoms or vomiting/regurgitation episodes.

*Erosive Esophagitis*

In an uncontrolled, open-label dose-titration study, healing of erosive esophagitis in pediatric patients aged 1 to 16 years required doses that ranged from 0.7 to 3.5 mg/kg/day (80 mg/day). Doses were initiated at 0.7 mg/kg/day. Doses were increased in increments of 0.7 mg/kg/day (if intraesophageal pH showed a pH of < 4 for less than 6% of a 24-hour study). After titration, patients remained on treatment for 3 months. Forty-four percent of the patients were healed on a dose of 0.7 mg/kg body weight; most of the remaining patients were healed with 1.4 mg/kg after an additional 3 months' treatment. Erosive esophagitis was healed in 51 of 57 (90%) children who completed the first course of treatment in the healing phase of the study. In addition, after 3 months of treatment, 33% of the children had no overall symptoms, 57% had mild reflux symptoms, and 40% had less frequent regurgitation/vomiting.

*Maintenance of Healing of Erosive Esophagitis*

In an uncontrolled, open-label study of maintenance of healing of erosive esophagitis in 46 pediatric patients, 54% of patients required half the healing dose. The remaining patients increased the healing dose (0.7 to a maximum of 2.8 mg/kg/day) either for the entire maintenance period, or returned to half the dose before completion. Of the 46 patients who entered the maintenance phase, 19 (41%) had no relapse. In addition, maintenance therapy in erosive esophagitis patients resulted in 63% of patients having no overall symptoms.

*Safety*

The safety of PRILOSEC Delayed-Release Capsules has been assessed in 310 pediatric patients aged 0 to 16 years and 62 physiologically normal volunteers aged 2 years to 16 years. Of the 310 pediatric

patients with acid-related disease, a group of 46 who had documented healing of erosive esophagitis after 3 months of treatment continued on maintenance therapy for up to 749 days.

PRILOSEC Delayed-Release Capsules administered to pediatric patients was generally well tolerated with an adverse event profile resembling that in adults. Unique to the pediatric population, however, adverse events of the respiratory system were most frequently reported in both the 0 to 2 year and 2 to 16 year age groups (46.2% and 18.5%, respectively). Similarly, otitis media was frequently reported in the 0 to 2 year age group (22.6%), and accidental injuries were reported frequently in the 2 to 16 year age group (3.8%).

### Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

## ADVERSE REACTIONS

PRILOSEC Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRILOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

| | Omeprazole (n = 465) | Placebo (n = 64) | Ranitidine (n = 195) |
|---|---|---|---|
| Headache | 6.9 (2.4) | 6.3 | 7.7 (2.6) |
| Diarrhea | 3.0 (1.9) | 3.1 (1.6) | 2.1 (0.5) |
| Abdominal Pain | 2.4 (0.4) | 3.1 | 2.1 |
| Nausea | 2.2 (0.9) | 3.1 | 4.1 (0.5) |
| URI | 1.9 | 1.6 | 2.6 |
| Dizziness | 1.5 (0.6) | 0.0 | 2.6 (1.0) |
| Vomiting | 1.5 (0.4) | 4.7 | 1.5 (0.5) |
| Rash | 1.5 (1.1) | 0.0 | 0.0 |
| Constipation | 1.1 (0.9) | 0.0 | 0.0 |
| Cough | 1.1 | 0.0 | 1.5 |
| Asthenia | 1.1 (0.2) | 1.6 (1.6) | 1.5 (1.0) |
| Back Pain | 1.1 | 0.0 | 0.5 |

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1%
Causal Relationship not Assessed

| | Omeprazole (n = 2631) | Placebo (n = 120) |
|---|---|---|
| *Body as a Whole, site unspecified* | | |
| Abdominal pain | 5.2 | 3.3 |
| Asthenia | 1.3 | 0.8 |
| *Digestive System* | | |
| Constipation | 1.5 | 0.8 |
| Diarrhea | 3.7 | 2.5 |
| Flatulence | 2.7 | 5.8 |
| Nausea | 4.0 | 6.7 |
| Vomiting | 3.2 | 10.0 |
| Acid regurgitation | 1.9 | 3.3 |
| *Nervous System/Psychiatric* | | |
| Headache | 2.9 | 2.5 |

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRILOSEC was unclear.

*Body As a Whole:* Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling
*Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema
*Gastrointestinal:* Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.
*Hepatic:* Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
*Metabolic/Nutritional*: Hyponatremia, hypoglycemia, weight gain
*Musculoskeletal*: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain
*Nervous System/Psychiatric*: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia
*Respiratory:* Epistaxis, pharyngeal pain
*Skin:* Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis
*Special Senses:* Tinnitus, taste perversion
*Ocular:* blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis, double vision
*Urogenital:* Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia

*Hematologic:* Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

### Combination Therapy for *H. pylori* Eradication

In clinical trials using either dual therapy with PRILOSEC and clarithromycin, or triple therapy with PRILOSEC, clarithromycin, and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with omeprazole, clarithromycin, or amoxicillin.

*Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)* — The most frequent adverse experiences observed in clinical trials using combination therapy with PRILOSEC, clarithromycin, and amoxicillin (n = 274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking the antimicrobial drugs alone.

For more information on clarithromycin or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.

*Dual Therapy (PRILOSEC/clarithromycin)* — Adverse experiences observed in controlled clinical trials using combination therapy with PRILOSEC and clarithromycin (n = 346) which differed from those previously described for omeprazole alone were: Taste perversion (15%), tongue discoloration (2%), rhinitis (2%), pharyngitis (1%) and flu syndrome (1%).

For more information on clarithromycin, refer to the clarithromycin package insert, ADVERSE REACTIONS section.

## OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been reported when PRILOSEC was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

## DOSAGE AND ADMINISTRATION

### Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of PRILOSEC is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

### *H. pylori* Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence

*Triple Therapy (PRILOSEC/clarithromycin/amoxicillin)* — The recommended adult oral regimen is PRILOSEC 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

*Dual Therapy (PRILOSEC/clarithromycin)* — The recommended adult oral regimen is PRILOSEC 40 mg once daily plus clarithromycin 500 mg t.i.d. for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNING, and for information regarding dosing in elderly and renally impaired patients (PRECAUTIONS: General, PRECAUTIONS: Geriatric Use and PRECAUTIONS: Drug Interactions).

Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS.

### Gastric Ulcer

The recommended adult oral dose is 40 mg once a day for 4 -8 weeks. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer, and INDICATIONS AND USAGE, Gastric Ulcer.)

### Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See INDICATIONS AND USAGE.)

### Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

### Pathological Hypersecretory Conditions

The dosage of PRILOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with PRILOSEC for more than 5 years.

### Pediatric Patients

For the treatment of GERD or other acid-related disorders, the recommended dose for pediatric patients 2 years of age and older is as follows:

| PATIENT WEIGHT | OMEPRAZOLE DOSE |
|---|---|
| < 20 KG | 10 MG |
| ≥ 20 KG | 20 MG |

ON A PER KG BASIS, THE DOSES OF OMEPRAZOLE REQUIRED TO HEAL EROSIVE ESOPHAGITIS ARE GREATER THAN THOSE FOR ADULTS.

For pediatric patients unable to swallow an intact capsule, see Alternative Administration Options subsection below.

### Alternative Administration Options

For patients who have difficulty swallowing capsules, the contents of a PRILOSEC Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

No dosage adjustment is necessary for patients with renal impairment or for the elderly.

PRILOSEC Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with PRILOSEC.

Patients should be cautioned that the PRILOSEC Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

## HOW SUPPLIED

No. 3426 — PRILOSEC Delayed-Release Capsules, 10 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 606 on cap and PRILOSEC 10 on the body. They are supplied as follows:

**NDC** 0186-0606-31 unit of use bottles of 30
**NDC** 0186-0606-82 bottles of 1000.

No. 3440 — PRILOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules, coded 742 on cap and PRILOSEC 20 on body. They are supplied as follows:

**NDC** 0186-0742-31 unit of use bottles of 30
**NDC** 0186-0742-82 bottles of 1000.

No. 3428 — PRILOSEC Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, apricot and amethyst colored capsules, coded 743 on cap and PRILOSEC 40 on the body. They are supplied as follows:

**NDC** 0186-0743-31 unit of use bottles of 30
**NDC** 0186-0743-68 bottles of 100
**NDC** 0186-0743-82 bottles of 1000.

### Storage

Store PRILOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 15°C and 30°C (59°F and 86°F).

## REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol, 20, No. 2, NCCLS, Wayne, PA, January 2000.

2. Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 200: 516.

3. Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;96(1):63-8.

4. Ruidómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150:476-81.

5. Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.

PRILOSEC is a trademark of the AstraZeneca group of companies.



Manufactured for: AstraZeneca LP, Wilmington, DE 19850
BY: MERCK & CO., INC., WHITEHOUSE STATION, NJ 08889, USA

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AstraZeneca

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-810/S-003 & S-058

# MEDICAL REVIEW(s)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW
OF LABELING CHANGES

| | |
|---|---|
| NDA: | 19-810, S-003<br>19-810, S-058 |
| Sponsor: | Astra Zeneca<br>1800 Concord Pike<br>Wilmington, Delaware |
| Date Submitted: | December 23, 2004 |
| Drug Name: | Prilosec (Omeprazole-Delayed Release Capsules) |
| Drug Class: | Proton Pump Inhibitor |
| Documents Reviewed: | Electronic Submission for Final Printed Labeling |
| Division Director: | Robert Justice, M.D., M.S. |
| Deputy Director: | Joyce Korvick, M.D., M.P.H. |
| Team Leader (Acting) | Ruyi He, M.D. |
| Medical Officer: | Lolita A. Lopez, M.D. |

## I. PROPOSED LABELING CHANGES

The Agency issued an approvable letter on October 3, 2003 regarding supplemental new drug application for Prilosec, S-058 and S-003.

The sponsor was advised that a final printed labeling (FPL) must be submitted with the Agency's recommended revisions before the application maybe approved.

In this submission, the sponsor has incorporated the Agency's recommendations to the package insert under **PRECAUTIONS:**

1) **Pregnancy** (S-058)

   Under **Teratology:** the sponsor has replaced the word "pregnancy" to "pregnant" rabbits.

2) **Nursing Mothers** (S-058).

   The sponsor has incorporated the recommended changes:

   *Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.*

## II. RECOMMENDATION

The proposed revisions to the package insert under PRECAUTIONS, Pregnancy, and Nursing Mothers are clinically acceptable.

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Lolita Lopez
2/4/04 12:56:23 PM
MEDICAL OFFICER

Ruyi He
2/4/04 01:19:11 PM
MEDICAL OFFICER

10/03/03

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

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**DATE:** 10/4/03

**FROM:** Joyce A Korvick, MD, MPH

DGCDP/ODE III

**SUBJECT:** **Director (Deputy) Summary Approval Comments**
**NDA 19-810 SE8-58 and SLR-003**

**APPLICANT:** Astra-Zeneca LP

**DRUG:** Prilosec ™ (omeprazole) Delayed-Release Capsules.

**DIVISION RECOMMENDATION:**

The proposed labeling is approvable pending final recommended changes in the label, based upon review of previous labeling recommendations and toxicology data.

**Labeling:**

The issues are well characterized in the Medical Officer Review and Toxicology Reviews. This is the culmination of several iterations of the label. The proposed wording under **Carcinogenicity, Mutagenicity, Impairment of Fertility** regarding a primary malignant tumor observed in a single rate is acceptable by both the clinical and toxicology reviewers (S-003). Previous changes made on January 30, 2003 regarding Nursing Mothers under the **PRECAUTIONS** sections were not made in the proposed label. It is again recommended that these changes be made.

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Joyce Korvick, MD, MPH
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products
CDER/FDA

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Joyce Korvick
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MEDICAL OFFICER

09/30/03

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW
OF LABELING CHANGES

| | |
|---|---|
| NDA: | 19-810, S-003<br>19-810, S-058 |
| Sponsor: | Astra Zeneca<br>1800 Concord Pike<br>Wilmington, Delaware |
| Date Submitted: | April 4, 2003 |
| Drug Name: | Prilosec (Omeprazole-Delayed Release Capsules) |
| Drug Class: | Proton Pump Inhibitor |
| Documents Reviewed: | Electronic Submission for Final Printed Labeling |
| Division Director: | Robert Justice, M.D., M.S. |
| Deputy Director: | Joyce Korvick, M.D., M.P.H. |
| Team Leader (Acting) | Gary Della'Zanna, D.O., M.Sc. |
| Medical Officer: | Lolita A. Lopez, M.D. |

## I. Draft Labeling Changes

The Agency issued an approvable letter on January 30, 2003 regarding supplemental new drug application for Prilosec, S-058 and S-003.

The sponsor was advised that a final printed labeling (FPL) must be submitted with the Agency's recommended revisions before the application maybe approved.

**A.** The sponsor has incorporated the Agency's recommendation to the package insert under **PRECAUTIONS:**

1) **Carcinogenicity, Mutagenicity, Impairment of Fertility** (S-003) regarding a primary malignant tumor observed in a single rat.

From a clinical standpoint, the proposed changes are acceptable. See Pharmacology Review for detailed comments.

2) **Pregnancy** (S-058)
Under Teratology…the sponsor should replace the word "pregnancy" to "pregnant" rabbits. Otherwise, the proposed labeling changes are acceptable, these were discussed with the Pharmacology Supervisor. See Pharmacology Review for details.

B. The sponsor needs to make the necessary changes regarding Nursing Mothers on the FPL under **PRECAUTIONS, Nursing Mothers** (S-058). The Agency recommends the following revision:

*Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.*

## II. RECOMMENDATIONS

1. From a clinical standpoint, the proposed labeling changes under: PRECAUTIONS, Carcinogenicity, Mutagenicity, and Impairment of Fertility regarding a primary malignant tumor observed in a single rat are acceptable.

2. The proposed revisions to the package insert under PRECAUTIONS, Pregnancy, are clinically acceptable. Under: Teratology…the sponsor should replace the word "pregnancy" rabbits to "pregnant" rabbits.

3. The sponsor should make the changes recommended by the Agency on January 30, 2003 regarding Nursing Mothers under section PRECAUTIONS.

   *Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious*

*adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.*

4. See Pharmacology Review for detailed comments.

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Lolita Lopez
9/30/03 10:22:09 AM
MEDICAL OFFICER

Gary DellaZanna
9/30/03 10:37:06 AM
MEDICAL OFFICER

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

FEB 8 2002

| | |
|---|---|
| NDA: | 19-810<br>SE8-058-AL |
| Date Submitted: | August 16, 2001 |
| Sponsor: | AstraZeneca (AZ)<br>Wayne, PA |
| Drug: | PRILOSEC® (omeprazole) |
| Formulation/Route of Administration: | Oral Delayed-Release Capsules |
| Pharmacological Category: | Antisecretory<br>Inhibitor of the $H^+/K^+$ ATPase enzyme System |
| Material Reviewed: | Resubmission-<br>Response to Approvable Letter |
| Reviewer: | Hugo E. Gallo-Torres, M.D., Ph.D.<br>Medical Team Leader, HFD-180<br>GI Drugs |

## I. BACKGROUND/SPONSOR PROPOSAL

In their initial submission of October 7, 1998 the sponsor proposed changes to the current approved labeling under the section **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy; and Nursing Mothers**. On August 4, 2000, the sponsor submitted a response to the Agency's October 7, 1999 not approvable letter. The supplement was approvable as per February 7, 2001 letter to sponsor. Requested by the Agency were final printed labeling with additional revisions to the package insert. This included the retention of the Pregnancy Category C classification.

Through the present letter, the sponsor is providing a response to the Approvable Letter. However, before providing FPL, the sponsor proposes deletion of the following paragraph, which appeared at the end of the second paragraph under the heading Pregnancy Category C.

"Sporadic reports have been received of congenital abnormalities occurring in infants, born to women who have received omeprazole during pregnancy. Omeprazole should be

used during pregnancy only if the potential benefit justifies the potential risk to the fetus".

## II. COMMENT

The proposed deletion of this text is acceptable because similar (actually improved) wording appears on the last two paragraph of the heading Pregnancy Category C.

> "Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

It is to be noted that the above text, proposed by the Agency, has already been accepted by the sponsor. Similarly, all other revisions proposed by the Agency under the heading Pregnancy Category C have been accepted by the sponsor.

## III. RECOMMENDATION FOR REGULATORY ACTION

The labeling revisions proposed by AZ under the heading **Pregnancy**
**Omeprazole**
**Pregnancy Category C**

are acceptable.

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader, HFD-180
GI Drugs

cc:
NDA 19-810/SE8-058-AL
NDA-180
HFD-180/VRaczkowski
HFD-180/JKorvick
HFD-180/HGallo-Torres
HFD-181/MWalsh
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Doris Garrison
2/8/02 02:59:12 PM
UNKNOWN

Hugo Gallo Torres
2/8/02 03:57:49 PM
MEDICAL OFFICER

**MEMORANDUM**

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

**DATE:** November 12, 2002

**TO:** **FILE: NDA 19-810/SE8-058**
**PRILOSEC® (omeprazole) Delayed –Release Capsules**
Sponsor :AstraZeneca LP
Wayne, PA
Dates of Submissions: July 31, 2002 and Auguast l6, 2002

**FROM:** Hugo E. Gallo-Torres, MD, PhD, PNS
Medical team Leader (GI Drugs)
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

**SUBJECT:** Amendment to pending Application: Amended Draft Labeling
This supplement provides for revision of the PRECAUTIONS section of the package insert to add preclinical information and clinical information from three epidemiological trials in pregnant women.

## I. BACKGROUNG

PRILOSEC® (omeprazole) is a Proton Pump Inhibitor (PPI) approved for a variety of indications for which profound and long-lasting inhibition of acid secretion is needed . Other PPIs available in the U.S. market are lanso-, rabe-, panto-, and esomeprazole. But the clinical experience with omeprazole is the largest and longest, since its approval in the late 1980s..In clinical practice, the PPIs are considered safe drugs, but questions still remain regarding their use in special populations such as pregnant patients and pediatric patients. Issues regarding the pregnancy section of the labeling are addressed here.

In the initially approved labeling, PRILOSEC is listed as *Pregnancy Category C.* Animal data are described showing that although the drug is not teratogenic, it is embryo (feto)- toxic. In addition, the initially approved label stated that there are no adequate and well-controlled studies in pregnant women. Mention was made that sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. The section ended with the recommendation that omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In supplement 058, dated October 7, 1998, the sponsor requested changing the pregnancy category from C to B.[ An NDA for the OTC treatment of heartburn, which requires addressing

the pregnancy issue, has also been submitted]. The sponsor's submission included results of three epidemiological studies addressing the safety of omeprazole for the developing fetus. Pregnancy information was reviewed by Dr. K. Robie-Suh (January 22, 1999). Consultation was provided by Dr. S. Kweder (September 23, 1999. After taking into consideration the information from these reviews in conjunction, the Agency decided to retain the Pregnancy Category C. A not approval letter, dated October 7, 1999, was issued. Revisions to the labeling were proposed to include preclinical information and clinical information from the three epidemiological studies in pregnant women. A resubmission dated August 4, 2000 was reviewed by Dr. Robie-Suh (February 7, 2001 ) and an additional resubmission, dated August 16, 2001, which represents the third review cycle of the drug, was initially reviewed and found acceptable by Dr. Hugo Gallo-Torres (February 8, 2002).
In the present resubmission, dated July 31, 2002, a follow up consult, dated October 8, 2002, was sent to the Pregnancy Labeling Team, Office of New Drugs, HFD-020.

In their consult review, dated October 30, 2002, the Pregnancy Labeling Team (PLT) suggests that the discussion of the sponsor-submitted epidemiological studies be more descriptive and provide more clinically relevant information that will assist health care providers and their patients when making decisions regarding the use of omeprazole in pregnancy. In summary, the PLT's recommendations include: 1) addition of information regarding the number of patients exposed; 2)maternal and fetal outcomes; and 3) citation of pertinent references.

## II. RECOMMENDATIONS FOR REGULATORY ACTION

The HFD-180 MLT recommends to accept the PLT's recommendations. The MTL agrees that these recommendations are more in line with the proposed pregnancy labeling rule and other updated pregnancy sections of product labeling that provide more clinically relevant information.

The MTL recommends to accept all edits to the pregnancy section on the PRILOSEC labeling proposed by the PLT and listed in Section **V. PROPOSED PREGNANCY LABELING** of the PLT consult review. These proposed labeling revisions reflect the PLT's recommendations for labeling.

cc:
Archival NDA 19-810/SE8-058
HFD-180/Div. Files
HFD-180/RJustice/JKorvick/KRobie-Suh/MWalsh/HGallo-Torres
HFD-020/SKweder/KUhl/DLKennedy

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/s/

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Hugo Gallo Torres
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MEDICAL OFFICER

MEMORANDUM

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

| | |
|---|---|
| DATE: | October 28, 2002 |
| TO: | Robert Justice, MD<br>Director, HFD-180 |
| THROUGH: | Sandra Kweder, MD<br>Deputy Director, OND, HFD-020<br>Chair, Pregnancy Labeling Task Force |
| FROM: | Kathleen Uhl, MD<br>Dianne L. Kennedy, RPh, MPH<br>Pregnancy Labeling Team<br>Office of New Drugs, HFD-020 |
| NDA: | 19-810 SE8-058 |
| Sponsor: | Astra Pharmaceuticals |
| Drug name: | Prilosec (omeprazole) |
| Submission date: | August 16, 2002 |
| Consult received: | October 10, 2002 |
| Due date: | November 12, 2002 |
| SUBJECT: | Protocol Number: 190168-051P-00 |

## I. EXECUTIVE SUMMARY

A consult was submitted to the Pregnancy Labeling team to review the pregnancy section of labeling submitted as part of the supplement for omeprazole. The label submitted in this supplement currently includes a brief description of 3 epidemiologic studies. The pregnancy labeling team suggests that the discussion of these studies be more descriptive and provide more clinically relevant information that will assist health care providers and their patients when making decisions regarding drug use in pregnancy. Our recommendations include information regarding the number of exposed patients, maternal and fetal outcomes, and citing the references, among others. The pregnancy section is edited in this consult to reflect these recommendations for labeling.

## II. INTRODUCTION

Revisions to the labeling for Prilosec (omeprazole) have been ongoing in the Division of Gastrointestinal and Coagulation Drug Products, HFD-180. This is the fourth review cycle for this NDA which includes revision of the PRECAUTIONS section of labeling. The sponsor had previously requested changing the Pregnancy Category from C to B and, as well as, submitted an NDA for the OTC treatment of heartburn. Dr. Sandra Kweder provided written consultation on

pregnancy labeling for this product, at the Division's request, completed 9/22/99, which is attached to this consult. Revisions to labeling for Prilosec include preclinical information and clinical information from three epidemiological studies in pregnant women. We are currently being consulted to review the proposed labeling under PRECAUTIONS, Pregnancy for final acceptability of the language regarding human data.

## III. BACKGROUND

The Pregnancy Labeling Team and Pregnancy Labeling Task Force have been working to improve labeling of drugs for use in pregnancy and lactation. The Pregnancy Labeling Team presented including a discussion of current activities and an overview of the proposed labeling rule to HFD-180 on September 10, 2002. The goal of the team's efforts is to enhance the clinical utility of labels regarding the use of drugs in pregnancy, taking into account that in some cases such use is elective and in others pregnancy occurs unknowingly while a patient is taking a medication. These two common types of exposure lead to very different clinical decision making pathways. Product labels should inform physicians in a manner that facilitates their consideration of what is known and what is not known about the risks of a given product in pregnancy.

Labels that illustrate recent experiences in CDER with revising existing labels to make them more informative regarding exposure during pregnancy are appended to this consult. In Fall 2001 during the bioterrorism anthrax episode, the Pregnancy Labeling Team worked with the Division of Anti-infective Drug Products (HFD-520) and the Division of Special Pathogens and Immunologic Drug Products (HFD-590) and pharmaceutical sponsors to upgrade the pregnancy section of labeling for doxycycline and ciprofloxacin. The pregnancy sections of labeling provide more clinical information including positive and negative experiences about the use of these products during pregnancy including addressing 1$^{st}$ trimester exposures.

A third pregnancy labeling example is included for the Division's information. The Pulmicort Turbohaler (budesonide) label was updated in 2001 and included information from the Swedish Medical Birth Registry and resulted in a change in pregnancy category from C to B. This labeling includes a description of the registry including the numbers of exposed infants and rates of malformations.

## IV. LITERATURE REVIEW

Four epidemiologic articles have been reviewed by the PLT for incorporation into the pregnancy section of labeling for Prilosec.

1. Källén BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. Eur J Obstet Gynecol Reprod Biol 2001;96:63-68.

3. Ruidómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. Am J Epidemiol 1999;150:476-81.

4. Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.

We reviewed reference databases (available in ) that provide information regarding reproductive toxicology:

1. TERIS – The Teratogen Information System
2. )
3. Shepard's Catalog of Teratogenic Agents

In addition there are several references that provide information about the use of single dose omeprazole as prophylaxis for aspiration during caesarean section. References 1-4 include infant outcomes at birth. Some references include:

1. Stuart JC, Kan AF, Rowbottom SJ, et al. Acid aspiration prophylaxis for emergency caesarean section. *Anesthesia* 1996;51:415-21.

2. Moore J, Flynn RJ, Sampaio M, et al. Effect of single-dose omeprazole on intragastric acidity and volume during obstetric anaesthesia. *Anesthesia* 1989;44:559-62.

3. Gin T, Weart MC, Yau G, et al. Effect of oral omeprazole on intragastric pH and volume in women undergoing elective caesarean section. *Br J Anaesth* 1990;65:616-19.

4. Ewart MC, Yau G, Gin T, et al. A comparison of the effects of omeprazole and ranitidine on gastric secretion in women undergoing elective Caesarean section. *Anesthesia* 1990;45:527-30.

5. Rocke DA, Rout CC, Gouws E. Intravenous administration of the proton pump inhibitor omeprazole reduces the risk of acid aspiration at emergency cesarean section. *Anesth Analg* 1994;78(6):1093-98.

## V. PROPOSED PREGNANCY LABELING

The Pregnancy Labeling team has reviewed the proposed label and the epidemiologic studies and proposes the following changes to the labeling:

**Pregnancy**
**Omeprazole**
*Pregnancy Category C*

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2-2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

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Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 200[illegible] 516.

Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during regnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;96(1):63-8.

Ruidómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150:476-81.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures)[1]. The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study had 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at doses up to 138mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatel developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

[1] Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.

## VI. CONCLUSIONS

Omeprazole is in its 4th review cycle and this application contains revision of the PRECAUTIONS section of labeling. The Pregnancy Labeling Team has reviewed the proposed pregnancy section of labeling and propose recommendations that are more in line with the proposed pregnancy labeling rule and other updated pregnancy sections of product labeling that provide more clinically relevant information.

Kathleen Uhl, MD

Dianne L. Kennedy, RPh, MPH

Pregnancy Labeling Team

## VII. ADDENDUM

*1. Updated Doxycycline Pregnancy Labeling:*
**Pregnancy: Teratogenic Effects. Pregnancy Category D:**
There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk[3].

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline.) This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases[4].

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age[5].

**Nursing Mothers**
Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown[6]. Because of the potential for adverse reactions in nursing infants from doxcycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS.**)

The following references to the list of references were added at the end of the label:
3. Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
4. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997;89:524-528.
5. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317.
6. Hale T. *Medications and Mothers Milk.* 9th. edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.

*2. Updated Ciprofloxacin Pregnancy Labeling:*
**Pregnancy: Teratogenic Effects. Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to
pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones-(52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, fetal distress, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (See **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See **WARNINGS**.)

**Nursing Mothers:** Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to

discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

The following references to the list of references were added at the end of the label:
7. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.
8. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6): 1336-1339.
9. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure . Evaluation of a case registry of the European network of teratology information services (ENTIS). Eur J Obstet Gynecol Reprod Biol. 1996;69:83-89.

***3. Updated Pulmicort Turbohaler (budesonide) Pregnancy Labeling and category change:***
*Pregnancy Category B*
"As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (approximately 1/3 the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis). No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m 2 basis). Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. Studies of pregnant women, however, have not shown that PULMICORT TURBUHALER increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2,014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8 % vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively). These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%). Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT TURBUHALER should be used during pregnancy only if clearly needed."

ATTACHMENT 1.

# Memorandum of Consultation

Date: September 21, 1999

From: Sandra L. Kweder, M.Ij>. Director (Acting)
Office of Drug Evaluat~on **IV** (HFD-IO4) Co-Chair, FDA Pregnancy Labeling Taskforce

To: Lilia Talarico, M.D.
Director
Di vision of Gastrointestinal and Hematologic Drug Products (HFD-180)

Subject: NDA 19-810 5-058
Omeprazole label: Pregnancy subsection

Consultation Request Date: 8/25/99
Requested Completion Date: 9/22/99

Original Consultation Request

*"In light of ongoing deliberations by the Pregnancy Labeling Task Force regarding the requirements for Pregnancy Category" we are requesting your assistance in answering the following questions: Are the human data contained in this supplement sufficient for labeling this drug as Pregnancy Category B? If not, what kinds of human data are needed to support a change in the Pregnancy Category from* C *to B? Are the sponsor's proposed revisions adding the results of the epidemiological studies adequate? What additional Pregnancy Category issues should we address?*

*"Please be aware that the sponsor is developing this drug for the OTC treatment of heartburn and plans to submit the NDA in February 2000. The NDA will be discussed at a Joint Advisory Committee mostly for safety issues one of which is that the prescription drug is labeled Pregnancy Category* C. "

Material Submitted in Consultation

1. Copies of email notes from Maria Walsh to Sandra L. Kweder, M.D. (2/2/99) and response (2/8/99).
2. Astra Pharmaceuticals cover letter to NDA 19-810 (SE8-058), dat~d 10/7/98, accompanied by proposed label changes.
3. Medical Officer Review of submitted data, dated 1/21/99.
4. Pharmacologist's Review of submitted data, dated 8/11/99.

Recommendations

1. It is essential that the pharm/tox data and the conclusions that can be drawn from them be stated clearly. From my reading packet, I find the preclinical data generally supportive of Category B designation on their own. I strongly recommend that Dr. Joseph De George, Associate Director of Pharmacology/Toxicology, Office of Review Management, be briefed on this drug and the issues presented by the new data.

2. The human data submitted might be adequate to support a change in category. The sponsor should be asked to consider obtaining original data and more detail from the provided studies, particularly the Motherisk study. If this can be done, then CDER' s epidemiology experts should review these and assist in providing confidence intervals around the results. In the absence of doing so, it might be more useful to simply be able to state in the label from these studies what magnitude of risk for endpoints of interest can and can't be ruled out. .

3. Regardless of whether the Pregnancy Category is changed information from the human studies should be summarized in the label to assist clinician's making therapeutic decisions about omeprazole for pregnant women. More importantly, the types of findings in the animal and human studies reported in this NDA make it essential that the information be clearly presented in a way that does not incite alarm in patients (or clinicians) faced with inadvertent exposure in pregnancy (i.e., when a woman has been taking omeprazole for some period of time prior to knowledge of her pregnancy).

4. Regardless of the Division's final decision about whether to grant the sponsor's request for a change to Category B from C, the sponsor should institute a pregnancy registry for this drug. I expect that with appropriate recruiting efforts it will not be difficult to enroll. A component of the registry that employs long term follow-up of children exposed for some minimum duration in utero should be instituted as well, based on carcinogenicity data.

I. Consultation Background

The NDA supplement submitted by Astra for the change of the Pregnancy subsection of labeling from Category C to Category B is proposed on the basis of several sources of information. First, the sponsor has submitted additional data to the preclinical toxicology database, predominantly from studies that predate the original NDA submission, but which were conducted in Japan and not previously translated into English. Second, the sponsor has provided information from three epidemiology studies in humans in support of the lack of any associated teratogenicity or adverse fetal effects of omeprazole when taken by pregnant women. Findings from these preclinical and clinical data sources are reviewed in the Pharmacology/Toxicology review and the Medical Officer review and will not be described in detail here. I will address the regulatory framework in which the issues arise for this

NDA; provide some general comment on the preclinical and epidemiology data and what it is reasonable to expect, and; provide recommendations.

II. Regulatory Framework: Pregnancy Categories

The regulations governing how to label drugs for use in pregnancy reside under CPR 201.57 (0 (6). Requirements set forth in this regulation for Pregnancy category Band C are as follows:

> ***Pregnancy Category B.*** If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the label shall state: "Pregnancy Category B....." If animal reproductive studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B….. " The labeling shall also contain a description of the human studies and a description of the available data on the effect of the drug on the later growth, development and functional maturation of the child.
>
> ***Pregnancy Category* C.** If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risk, the labeling shall state: "Pregnancy Category C. ..." If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C..." The labeling shall contain a description of any available data on the growth, development, and functional maturation of the child.

For practical purposes, the distinctions between categories C and B lie in two areas. The first is how worrisome the animal data are. Animal data that show no adverse effect or an effect which, in the judgment of the pharmacology/toxicology (pharm/tox) reviewer, is of minimal concern, have historically been considered to warrant assignment of Category B. An example might be when an effect on the fetus is seen that is considered to be directly related to maternal impairment or toxicity (e.g., the dam in animal studies at high doses often displays general signs of toxicity from the drug administered, leading to poor weight gain with secondary effects on the fetus). Animal data that clearly indicate an effect on the fetus that can not be attributed to maternal toxicity, but point directly to the drug itself being the culprit are assigned Category C. Unfortunately, many drugs lie in an ill-defined area of uncertainty that make it unclear whether they warrant a B or a C designation. In such cases, the predictive value of the animal species in which the finding occurs, the relevance of the finding to humans and the pharmacology of the drug must be taken into account in deciding which category to assign.

The second area of distinction relates to how much clinical data are available. While the CFR indicates that data from adequate and well-controlled studies are required, it does not

go further in describing what that standard is for the purpose of pregnancy labeling. It is reasonable *to* assume that the broad spectrum of "adequate and well-controlled" that applies to most review activities of the FDA does here as well. This could include studies of a dose-response nature; randomized comparative controlled trials; historical controls; etc. Within this broad framework, the standard imposed must take into account the likelihood of being able to collect data in any given setting, as well as what the purpose of seeking the data is.
In the case of pregnancy labeling, data collection is pursued in order to obtain some margin of reassurance that the drug is reasonably likely to be safe (i.e., not inherently dangerous), keeping in mind that absolute safety can never be assured. Further, "pregnancy" is no*t* a separate indication, so the standard typically imposed for approval of new indications (most commonly randomized, controlled clinical trials) is not appropriate. Therefore, *it* seems that epidemiology studies, when well conducted, can provide sound reassurance and meet the requirement for adequate and well controlled studies.

III. Preclinical Data

In the original NDA review and resultant label, the major concern from the reproductive toxicity studies was embryolethality and fetal resorptions in rabbits administered omeprazole (doses equivalent to 17 to 172 times the human standard dose). In rats, dose related embryo/fetal toxicity and postnatal toxicity were observed when parents were treated with omeprazole at doses 35 to 345 times the human standard dose.

The newly submitted studies reviewed in this NDA supplement appear to have been submitted in order to provide convincing data that these toxicities were most likely due to maternal toxicity. In general, the findings of these recently submitted studies do offer a much less worrisome picture of omeprazole than is currently described in the product label. The pharm/tox review by Dr. Robinson from HFD-180 describes concerns about whether the additional data were from studies that met Good Laboratory Practice (GLP) standards. It also raises concerns in many of the studies regarding the lack of full accounting for the pregnancy outcomes (i.e., numbers of implantations, live born fetuses and still born fetuses), although the numbers missing were small in most cases.

It is unclear from the pharm/tox review whether the label changes proposed by the sponsor, which conclude that adverse effects seen in these in utero exposure studies were the result of maternal toxicity, would be acceptable if the sponsor could address the GLP issue and fetal accounting satisfactorily. This is a critical matter to resolve. If so, it would seem that the change from Pregnancy Category C to Pregnancy Category B could be made entirely on the basis of preclinical data, with the human data provided only as supplemental information.

IV. Clinical Data

The sponsor submitted three human 'epidemiology studies that address the safety of omeprazole for the developing fetus, These studies are described and critiqued in the medical officer's review by Dr. Robie-Suh. For sake of brevity, I will highlight relevant points about each, below.

A. *United Kingdom and Italy Epidemiology Study: Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes.*

This study was conducted using the U.K. General Practice Research Database (GPRD) and a birth registry and prescription database from a region in northern Italy. The GPRD is one of the most complete clinical practice/research databases in the world and is highly sought after for studying drug safety issues. It has been used for studies of pregnancy outcomes in the past. It has a long record of validated data and methods. Less is known about the Italian registry and prescription database. Both data sources included a control group of unexposed women. Endpoints assessed were structural malformations detectable at birth (whether live or stillbirth) and out to one year. There were 5 reports (among 134 omeprazole exposed mother- infant pairs) of congenital anomalies. These were tongue tie (1); cardiac septal defect (2); dysplastic hip/click (1); inguinal hernia (1). There was no significant difference in pattern or in rates of findings between omeprazole-exposed patients and controls.

Strengths of the study:

- The GPRD is a well known and potentially powerful database that is considered reliable for conducting epidemiology studies of drug safety, including those addressing pregnancy outcomes.
- Non-exposed controls were included for both the U.K. and Italy site.
- Endpoints could be reported as late as one year after birth.

Weaknesses of the study:

- The numbers of patients exposed to omeprazole is very small (97 in GPRD; 37 in Italy).
- Spontaneous abortions were not included in the study, an endpoint that would be of interest based on animal data.
- It is impossible to tell from the data how many women received combinations of omeprazole and an H2-blocker.
- The results of the study do not clearly distinguish exposures by timing in pregnancy, although the methods of the study indicate that doing so is potentially possible. However, the number of events is so small and types of events are quite variable, making this less of an issue for this study.

Consultant's Comment: As described by the medical officer who reviewed the study, it appears that with the small number of exposures and events in this study only a large risk of anatomic malformations can be ruled out, i.e., the risk is not likely to be greater than 7 per 1,000 exposures. This is not much different than the background rate of congenital anomalies in western countries, generally estimated at 4-6 per 1,000 live births.

B. *Swedish Epidemiology Study: Delivery' outcomes after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole.*

This retrospective cohort study was conducted through the Swedish Medical Birth Registry over a two year period. Congenital malformations and various standard measures of fetal growth and development were extracted from the records linked to this database. Omeprazole exposure was reported for 262 women of 200,000 births. The control group was non-exposed mothers from the same database. There were some differences between the exposed and non-exposed cohorts (the former had an increased use of concomitant medications; were older and tended to smoke more). Eight abnormalities were reported among the 262omeprazole mother-infant pair. These included: ventricular septal defect (3); patent ductus arteriosus (1); unspecified cardiac defect (1); urethral valve (1); facial anomaly (1); Down Syndrome (1). Overall, the numbers and rates of events was not significantly different for the omeprazole group compared to controls or other acid suppressant exposed groups.

Strengths of the study:

- This national registry has been in existence for many years and is not likely to be subject to systematic bias.
- An attempt was made to capture and analyze women who were exposed to more than one acid-suppressing drug.

Weaknesses of the study:

- No doses or duration of exposures to omeprazole were reported.
- Once again, rates of spontaneous abortions were not assessed.
- The rates of events only address combined malformation rates. No attempt is made to quantify rates of individual system malformations, for example. This is often a futile exercise when overall event rates are small. However, it is interesting in this study that half of the anomalous findings in the omeprazole group were cardiac structural abnormalities.

Consultant's Comments: Once again, the event rate in this study was not large. The findings of cardiac structural abnormalities in the omeprazole exposed group is unlikely to be significant, but should be addressed.

C. *Motherisk EpidemiologyStudy:* A *preliminary report on the safety of omeprazole during pregnancy.*

Motherisk is the oldest and most sought after teratogen information service in the world. Patients who call the service for information are offered enrollment into cohort studies. This study included all calls for omeprazole exposure to Motherisk since its inception and calls to several similar systems in Europe. The authors report on 113 omeprazole exposures (59 from Toronto), with over a third also taking other antacid medications or pro-kinetics. Most exposures (nearly 90%) were in the first trimester. Overall malformation rates were similar for omeprazole treatment groups and disease-paired controls. There was a numerically higher rate of spontaneous

abortions in the omeprazole group (14%), versus 8% in the disease-paired controls and 8% in the non-teratogen treated group, which was not statistically significant.

Strengths of the study:

- As indicated, the Motherisk group has a long history of conducting such studies.
- Spontaneous abortions were assessed.
- Most exposures were identified as first trimester. This is still not detailed as one would like, but in epidemiology studies, is a step in the right direction.

Weaknesses of the study:

- The pooled nature of the data across several different systems is concerning without reassurance that collection and follow-up methods were indeed identical.
- Once again, overall, the numbers of exposures are small, making any differences between treatment groups and outcomes, other than those that are dramatic, unlikely to be detected.

Consultant's Comments: In general, this data source has the potential to offer more detailed information. Motherisk maintains very detailed records of its enrollees, and some of the questions about dosing and exposure raised by the medical officer's review might be able to be addressed by the investigators, particularly at the Toronto site.

*D. Spontaneous Reporting System and Other Sources*

The medical literature does not offer much additional information to what is described, above. The sponsor's reports of the findings from spontaneous reports also are not especially helpful (3 cases of general heart defects and 4 cases of anencephaly and other assorted findings).

V. General Comments

1. Overall, the studies presented, while limited, do not raise strong concerns about omeprazole being a drug that has a substantial risk of inducing congenital malformations when taken in pregnancy. In addition, the preclinical data available do not suggest a risk of specific congenital malformations. Certainly a small risk cannot be excluded from these data, but a high risk seems unlikely.

2. The data do not address the risk of embryolethality, with the exception of the study by the Motherisk group that, with small numbers of exposures, concluded there was no statistically significant increase in the rate of spontaneous abortion. This is an extremely difficult endpoint to study in any of the settings employed in these studies, as many spontaneous abortions will occur prior to knowledge of the woman that she is pregnant or even seeks testing for pregnancy.

3. Certainly the studies described do not constitute the type of data that one normally expects to see in controlled clinical trials of a new drug. From that standpoint it is

tempting to conclude that they are not "adequate and well controlled trials." On the other hand, the regulatory definition of adequate and well controlled is, in fact, quite broad, leaving substantial discretion to the FDA in this regard. When appropriate, historical controls or epidemiology data can be considered to meet the standard, as this is sometimes all that is available.

4. Given the above, it seems reasonable to expect that sound epidemiology studies could fit the bill of adequate and well controlled studies for purposes of assessing safety in pregnancy. This is particularly the case as the likelihood of enrolling and completing a randomized controlled trial of a drug to treat an indication that is not specific to pregnancy in pregnant women, with a size that has adequate power to detect differences in pregnancy outcomes of interest, is remote. The barriers to such a study are overwhelming, from simple numbers of available patients to IRB and legal issues. While many believe such studies are ethical and reasonable, the only disease in which studies like this have been successfully completed is hypertension -and only once to my knowledge, for

5. The studies reported by the sponsor do have limitations. However, it may be possible to put confidence intervals around the differences detected between treatments and controls. It may also be possible to obtain additional information about the data itself, such as information on timing of exposure, etc., before reaching final conclusions. I suggest that the Motherisk data would be the most fruitful for this purpose. Doing so would likely require a major clinical amendment to the NDA or, more likely a new submission if it is ultimately deemed necessary to have.

6. An additional study that could be undertaken by the sponsor, particularly if their interest is in obtaining an OTC indication, is a rigorous pregnancy registry. CDER has recently issued a Draft Guidance Document for Industry on Establishing Pregnancy Registries that could provide the sponsor with some basic information on where to begin their planning. Certainly such a registry should be required for the product if it is given OTC status, as exposures will likely increase and the need to have more detailed information will be important. Whether it should be required prior to OTC switch is a review issue that I suggest would be appropriate for an advisory committee to address.

7. It is of note that dosing in pregnancy is not addressed in any of the materials I have available for review. If a drug is expected to be used widely by pregnant women, it would seem reasonable that the sponsor would conduct some studies assessing its pharmacokinetics and tolerance in pregnancy. Or, in the absence of such formal studies, an attempt could be made to extrapolate animal PK data from pregnant and nonpregnant dams to humans, with subsequent confirmation in at least a few patients taking the drug for appropriate therapeutic indications during pregnancy.

8. It is also of note that the carcinogenicity concerns raised for omeprazole have not been addressed by the sponsor in terms of their relevance to exposure in utero. This may already have been discussed by HFD-180 in previous reviews.

9. As a general comment, it is not essential that a product carry a Pregnancy Category designation of B or A in order to obtain OTC status. A recent case in point are nicotine replacement products which are Categories C and D, to say nothing of alcohol or cigarettes which would likely carry Category D (or X) designation if they were drugs under FDA jurisdiction.

10. Overall, I agree that the findings of the data in this package suggest that there should not be great worry associated with the use of omeprazole in pregnancy, at least in the short term. Whether the drug is a Category B or a Category C is less important than describing the data that exist well to facilitate clinical decision making.

**Copies:**

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|---|---|
| NDA | 19-810 SE8-058 |
| HFD-020 | Kweder, Kennedy, Uhl |
| HFD-180 | Justice, Korvick, Gallo-Torres, Walsh |

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

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/s/

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Kathleen Uhl
10/29/02 04:46:30 PM
MEDICAL OFFICER

Sandra L. Kweder
10/30/02 01:49:14 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

| | | |
|---|---|---|
| NDA: | NDA 19-810 (SE8-058AZ) | FEB 7 2001 |
| Sponsor: | Astra Merck, Inc. | |
| Drug name: | Prilosec (omeprazole) Delayed-Release Capsules | |
| Date submitted: | August 4, 2000 | |
| Date Received: | August 7, 2000 | |
| Review completed: | February 7, 2001 | |
| Reviewer: | Kathy M. Robie-Suh, M.D., Ph.D. | |

**Background:**
Omeprazole is a substituted benzimidazole compound that inhibits gastric acid secretion by irreversibly binding to the gastric proton pump. It was approved in 1989 for treatment of severe erosive esophagitis, poorly responsive gastroesophageal reflux disease (GERD) and pathological hypersecretory syndromes. Additional subsequently approved indications include symptomatic GERD, healing and maintenance of erosive esophagitis, and healing of benign gastric and duodenal ulcers. Because animal studies in rats and rabbits showed fetal toxicity, the drug is classified as Pregnancy category C.

On October 7, 1998 the sponsor submitted a supplement to request a change in the pregnancy classification of the drug to Pregnancy category B and to support revisions to the **Precautions** section of the Prilosec labeling. The supporting material consisted of three independent epidemiological studies (2 retrospective) of the use of omeprazole during pregnancy conducted in Sweden, Canada and the United Kingdom and Italy. While most of the omeprazole-exposed mothers in these studies gave birth to normal infants, the studies were lacking in information about omeprazole dose/duration, compliance and concomitant medications and were not designed to allow reliable assessment of the relationship between omeprazole use and pregnancy outcome. Because of lack of adequate information to evaluate fetal risk from omeprazole exposure during pregnancy the change in Pregnancy category classification was not approved and the sponsor was asked to plan a prospective, controlled study of omeprazole in women having a serious medical need for the drug during pregnancy. (See Medical Officer's Review dated 1/22/99, Division's not approvable letter to the sponsor dated 10/7/99 and Division's letter to the sponsor dated 10/21/99).

In the current submission the sponsor responds to the Division's not approvable letter.

**Material Reviewed:**
The current submission consists of additional data and analyses from the Swedish study and some reanalysis of the previously submitted post-marketing spontaneous reports of fetal abnormality data. No new preclinical information is provided. The sponsor includes the original proposed text of labeling that was provided in the original supplement. Further, the sponsor

asserts that a prospective epidemiology study such as proposed by the Agency "is not possible to enroll or conduct at this time".

The sponsor's response and the previous information from the three epidemiology studies also have been reviewed by outside consultants Special Government Employees: Samuel Shapiro, M.D., Boston University; Lewis B. Holmes, M.D., Massachusetts General Hospital; and Adolfo Correa, M.D., Ph.D., Center for Disease Control and Prevention. (See Memorandum to NDA 19-810/S-058 from M.R. Walsh, Regulatory Project Manager, dated 10/16/2000)

**Summary of Additional Information:**
*Updated Swedish Epidemiology Study:* An additional 700 deliveries to omeprazole-exposed women were added to the database for this study from 1997-1999. The sponsor presented and summarized the results for the total database for this study. Also included is a manuscript by B. Kallen titled "Use of Omeprazole During Pregnancy – No Hazards Demonstrable" [not dated] (NDA Vol. 181.1, Attachment 4.1). [Note: The application summary of the Swedish Registry study appears to contain more data than the Kallen manuscript].

This was a retrospective cohort study intended to examine delivery outcome after maternal use of acid-suppressing drugs during early pregnancy. For this submission the sponsor has updated the database to include women in the Swedish Medical Birth Registry giving birth from 1995 through 1999. (The 10/7/98 submission contained data from 1995 through early 1997). Maternal drug use was identified by patient interview. Outcome measures assessed included presence of congenital malformations, gestational duration, birth weight, body length, head circumference, low Apgar score at 5 minutes and infant survival. Congenital malformations were further explored by linkage with the Register of Congenital Malformations.

*Results:* From 1995 through 1999 the Swedish Pregnancy Registry has documented 982 women who had omeprazole exposure during pregnancy; 853 of these were exposed in the first trimester and 129 after the first trimester. About 405,856 births total were recorded in the Registry during this time. Among these pregnancies there were / /infants born / / with first trimester exposure; 131 with exposure after first trimester). There were 24 twins. Twenty-six infants (2.5%) had malformations and there were 5 (0.6%) perinatal deaths. Results from the previous submission (10/7/98) and the current submission are summarized in the following table:

**Congenital Deformities and Other Fetal Adverse Events in the Swedish Registry Study**

| | Data from previous submission (1995-early 1997) | Total database (1995—1999) |
|---|---|---|
| Total Births | About 200.000 | 405.856 |
| Total exposed to omeprazole: | | |
| Deliveries | 282 | 982 |
| Infants | | |
| Twins | | 24 (2.4%) |
| Malformations | 9 | 26 (2.6%) |
| Perinatally dead | | 6 (0.6%) |
| First trimester exposure: | NP | |
| Deliveries | | 853 |
| Infants | | |
| Twins | | 20 (2.3%) |
| Malformations | | 21 (2.5%) |
| Perinatally dead : | | 5 (0.6%) |
| After first trimester exposure: | NP | |
| Deliveries | | 129 |
| Infants | | 131 (100%) |
| Twins | | 4 (3.1%) |
| Malformations | | 4 (3.1%) |
| Perinatally dead | | 1 (0.8%) |

NP= not provided

Reviewer's table

Among infants born to women with first trimester exposure to omeprazole about 3.2% had low birth weight and 0.5% had low Apgar score. Among women with omeprazole exposure after the first trimester 3.8% (5/131) had low birth weight and 0.8% had low Apgar score. For the total registry population the prevalence of congenital malformations was 3.5%. Omeprazole exposed infants had no significant increase in risk for any malformation or for any cardiovascular defect after stratification for year of birth, maternal age, parity and maternal smoking. Many infants with congenital abnormalities also had other first trimester drug exposures. The sponsor's table below summarizes the malformations seen in infants with exposure to omeprazole during the first trimester omeprazole:

**TABLE 4.**
**Distribution of Malformations According to First Trimester Exposure (Sweden)**

| Congenital Malformation | Number Observed | Other Drugs Used |
|---|---|---|
| Ventricular septal defect | 5 | 1-ergotamine, diazepam, propranolol<br>2-salbutamol |
| Persistent ductus arteriosus | 2 | None |
| Unspecified cardiac defect | 2 | 1-norfloxacin, ranitidine, sucralfate |
| Hypospadias | 1 | ranitidine |
| Hydronephrosis | 2 | 1-citalopram, carisoprodol, cetirizine, oral contraceptives |
| Pylorostenosis | 2 | 1-Antacids<br>2-sucralfate |
| Jejunal atresia | 1 | None |
| Urethral stenosis | 1 | Iron and vitamins |
| Bladder exstrophy | 1 | None |
| Plagiocephaly | 1 | Ranitidine |
| Facial anomaly | 1 | Meclozine |
| Down syndrome (mother 34 years) | 1 | None |
| Multiple malformation (Tetralogy of Fallot, eye malformation) | 1 | None |
| Nevus | 1 | Paracetamol |
| Total | 23 | |

Sponsor's table

*Total Epidemiology Database for Women Exposed to Omeprazole During Pregnancy:*
The table below summarizes the prevalence of various outcomes following omeprazole exposure during pregnancy in the three epidemiology studies:

**Prevalence of Various Fetal Outcomes following Omeprazole Exposure During Pregnancy**

| | UK/Italy | | Canada | | Sweden | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Omeprazole | Reference Group | Omeprazole | Reference Group | Omeprazole | Reference Group | Omeprazole | Reference Group |
| Fetal/Perinatal Deaths[a] | 3/237 (1.3%) | 15/1575 (0.9%) | 16/113 (14%) | 14/226 (6.2%) | 6/994 (0.6%) | 2029/405,856 (0.5%) | | |
| Pre-Term Deliveries | 11/139 (8.0%) | 115/1560 (7.3%) | 8/84 (9.5%) | 25/189 (13%) | NA | NA | 19/223 (8.5%) | 140/1749 (8.0%) |
| Low Birth Weight | 3/139 (2.2%) | 36/1560 (2.3%) | NA | NA | 32/994 (3.2%) | 12,987/405,85 6 (3.2%) | 1133 (3.1%) | 13,023/407,41 6 (3.2%) |
| Congenital Malformation[b, c] | 5/139 (3.6%) | 95/2142 (4.4%) | 4/78 (5.1%) | 5/164 (3.0%) | 22/863 (2.5%) | 14,528/405,85 6 (3.5%) | 31/1080 (2.9%) | 14,628/408,16 2 (3.6%) |

[a] UK/Italy – stillbirths, pregnancy loss after 28 weeks gestation; Canada – spontaneous abortions; Sweden – stillbirths and deaths during the first week of life

[b] omeprazole exposure during first trimester of pregnancy

[c] Reference groups – UK/Italy – non-exposed and H2 blockers; Canada – H2 blockers and other non-teratogenic agents; Sweden – all births in the Swedish Medical Birth Registry 1995-1999

sponsor's tables, modified

In the Canada study the sponsor found a statistically significant increase in spontaneous abortions in the omeprazole group compared to the two reference groups combined (14% vs. 6.2%; p-value=0.015); but this was not considered clinically meaningful because the background rate of clinical abortions in clinically recognized pregnancies in the general population is about 15%. Also, of the omeprazole exposed patients experiencing spontaneous abortion, 2 patients had scleroderma (a systemic connective tissue disorder that is associated with increased risk for miscarriage) and another had used cytotoxic drugs during the first trimester of pregnancy. No statistically significant differences in event prevalence between omeprazole and reference groups were seen for any other endpoints in any of the studies. The sponsor identified background rates in the general population of 10% for pre-term deliveries and 4-7% for low birth weight (<2500gm). The sponsor estimates that for congenital malformations the combined analysis from these studies had sufficient power to rule out a doubling of all malformations detected at birth and also to rule out a doubling of specific malformations occurring at a frequency of 1/1000 live born infants.

*Spontaneous Post-Marketing Reports:*
The sponsor has provided additional analysis of the spontaneous post-marketing reports through March, 1998. [Note: This is the same period of time covered in the previous submission; see Medical Officer's Review dated 1/22/99]. The sponsor's spontaneous reports adverse events database through 3/31/98 identified about 39 reports (22 patients) of omeprazole exposure during pregnancy where the fetus or infant had an identifiable adverse outcome; 34 reports were retrospective (i.e., received when the pregnancy outcome is known). Only two malformations were reported in more than two infants: anencephaly (4 cases) and general heart defects (3 cases). There were 16 cases of miscarriages and fetal demise (6 during first trimester, 3 second trimester, 3 stillbirths, 1 ectopic pregnancy, and 3 of unknown gestational age). There were 4 cases of maternal decision to terminate the pregnancy and one case of abortion following an overdose of omeprazole and "psychiatric problems". No fetal malformations were noted in these cases. The sponsor states that for 48 cases of omeprazole use during pregnancy, the outcome of the pregnancy was unknown and in 36 cases a healthy infant was delivered.

The sponsor provided the following estimates for omeprazole therapy and pregnancy among women in the U.S. during 1999 (based on IMS databases and normalizing value to the prevalence of pregnancy among women in various age ranges based on National Survey of Family Growth for U.S.).

**TABLE 10.**
**Omeprazole Therapy and Pregnancy Among US Women**

| Age of US Women | # Courses Omeprazole Therapy (Thousands)[a] | Pregnancy Rate (%)[b] | # Pregnancies per course of therapy |
|---|---|---|---|
| 15-20 | | 9% | |
| 21-25 | | 16% | |
| 26-30 | | 15% | |
| 31-35 | | 10% | |
| 36-40 | | 4% | |
| >40 | | 1% | |
| Unspecified | | 9% | |
| Total | | -- | |
| Expected 15-45 | | 9% | |

[a] Number of courses of therapy to women in the United States during 1999 in the indicated age ranges.

[b] Annual prevalence of pregnancy among women in the United States based on NSFG data.

Sponsor's table

The maximum number of at risk pregnancies in the U.S. was estimated at 729,540; however, taking into consideration that most omeprazole use is in women older than 35 years (where the pregnancy rate is lower), the sponsor calculated that a more realistic figure for women at "at risk" was 254.750 patients.

**Summary of Consultants' Comments:**

*Samuel Shapiro, MB, FRCP(E), Emeritus Director, Slone Epidemiology Unit, Boston University, Visiting Professor of Epidemiology, Columbia University:*

Based on the evidence available, Dr. Shapiro judged that there is no biological plausibility to the general hypothesis that omeprazole has adverse effects on pregnancy outcomes. There are no apparent grounds on which to be more concerned about adverse pregnancy outcomes in relation to omeprazole than in relation to other drugs in general, or to the $H_2$-receptor antagonists in particular. Epidemiologically, the available evidence is reassuring and suggests that omeprazole does not increase the overall risk of malformations and large scale prospective studies are not needed. Such studies would not likely be informative regarding the risk of specific malformations. Regarding possible increased risk of spontaneous abortions in pregnant women receiving omeprazole, Dr. Shapiro concluded that the limited data do not suggest an increased risk of spontaneous abortion in these patients. He acknowledged that there were deficiencies in the precision of the omeprazole exposure information and other data in the studies but concluded that while the studies were not ideal, the information collection was probably adequate. Dr. Shapiro did not recommend any further prospective study of women exposed to omeprazole during pregnancy and stated that such studies if done would be useful only for looking further at relatively common outcomes, such as overall malformation risk and short term deliveries. He also concluded that the evidence does not suggest a greater need for the surveillance of omeprazole, as opposed to $H_2$ blockers.

*Lewis B. Holmes, M.D., Genetics and Teratology Unit, Pediatric Service, Massachusetts General Hospital, Boston, MA 02114:*
Dr. Holmes examined and evaluated 20 adverse event reports (provided by FDA Division of Drug Risk Evaluation from the spontaneous reporting database) of infants exposed to omeprazole during pregnancy. These cases occurred from 1991 through 1996 and included: anencephaly (4 cases), cardiac deformities (ventricular septal defect, hypoplastic left heart), foot deformity (talipes, clubfoot), facial deformity, cleft palate, maxillary fibrous dysplasia, "oculo-auriculo-fronto-nasal syndrome", limb deformity, hydrancephaly, microcephaly, meningomyelocele, anophthalmia and hydrops, pyloric stenosis, Duane strabismus, fetal death, chromosomal rearrangement, hypoglycemia and metabolic acidosis.

In evaluating these cases Dr. Holmes used criteria which he has used previously in evaluating the frequency of major malformations in the surveillance of major malformations in a consecutive population of 200,000 newborn infants (Nelson K and Holmes LB. N. Engl. J. Med. 320:19-23 (1989)) and which are currently being used in the North American AED (antiepileptic drug) Pregnancy Registry evaluation of teratogenic potential of antiepileptic drugs. Dr. Holmes concluded that he could not consider any of the reported cases as being related to omeprazole. The outcomes were more reflective of the types of malformations that occur spontaneously and were illustrative of the more severe end of the spectrum. As factors complicating the evaluation of causality he noted that: almost all of the infants had significant exposures to other drugs; two infants had co-existing problems (maternal insulin-dependent diabetes; complex chromosome abnormality) that were more likely to have caused the outcome and; the number of cases was small and the amount of dose and exposure duration information was limited. He did not make any recommendations for further evaluations.

*Adolfo Correa, M.D., Ph.D., Acting Chief, Surveillance and Epidemiology Section, Birth Defects and Pediatric Genetics Branch, Division of Birth Defects, Child Development, and Disability and Health, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway, NE MS F-45, Atlanta, GA 30341:*
Dr. Correa felt that all three of the epidemiology studies had important strengths, mainly that the cohort design allowed an independent assessment of both exposure and outcome. The Swedish study also had the advantage of prospective collection of drug use data including trimester of exposure from a Medical Birth Registry that included all births; however, there was no information on spontaneous abortions. Also, there was limited information on the completeness of ascertainment of cases of malformations and no frequency distribution for congenital malformations in the reference population was provided. He concluded that the size of the study may have allowed detection of a moderate increase in the rate of all malformations in the cohort compared to all births, but the study was too small to detect an increased risk of any specific malformation (which is what most teratogens usually cause).

Dr. Correa identified a number of deficiencies of the Canadian study. The study cohort included only pregnant women counseled by teratogen information centers, so the population is somewhat selected. Also, there was considerable use of multiple drugs during pregnancy in this population. Information was collected retrospectively and ascertainment of malformations did not appear to be uniform. The study did have the strength of collecting data on an evaluation of several pregnancy outcomes, including spontaneous abortions; however, because of the limited size of the comparison groups, the study had very limited power to detect a difference in outcomes between the groups. Similarly, for the UK/Italy study there were issues of differences in case ascertainment (between the UK and Italian cohorts) and the exposed groups were small in size, resulting in a limited power to detect an overall increased risk for

congenital malformations. Also, it was not possible to evaluate potential confounders such as maternal age, family history of congenital abnormalities and use of multivitamins.

Dr. Correa concluded:

> "These retrospective cohort studies provided no evidence for an increased risk of congenital malformations or other pregnancy outcomes in relation to omeprazole use during the first trimester of pregnancy. However, findings from these studies are difficult to interpret in light of several methodological issues, including: potential selection bias related to the exclusion of spontaneous abortions and pregnancy terminations due to prenatal diagnoses of congenital malformations; limitations in case definition, ascertainment, validation, and classification; potential confounding; and inadequate power to detect increased risks for specific malformations (e.g., cardiac septal defects) or other specific pregnancy outcomes."

Regarding the 20 spontaneous reports of congenital malformations, Dr. Correa noted that 2 cases (fetal death and hypoglycemia/respiratory distress/pneumonia) actually were not "congenital birth defects" and 4 of the cases had other risk factors for congenital malformations (maternal diabetes, febrile illness, family history). Because of the spontaneous nature of these reports, there is no way of estimating the rate of adverse events among exposed and unexposed pregnancies, and of determining whether the adverse events among exposed pregnancies represent more than the expected number of events.

Dr. Correa provided comments and recommendations on the design of a prospective epidemiology study of women exposed to omeprazole during pregnancy. (See attached Appendix). However, he states that implementation of such a prospective cohort study of pregnant women exposed to omeprazole, or to any other single drug, is likely to require extensive resources and be prohibitively costly and inefficient. He suggested that a more useful approach would be to establish a post-marketing surveillance network that would provide surveillance for a number of prescription and non-prescription drugs over an extended period of time using standardized procedures and methods. However, he also concluded that this alternative approach would require extensive resources.

**Reviewer's Comments and Recommendations:**
Though the further information presented in this application expands the pregnancy safety database for omeprazole, it still does not constitute "adequate and well-controlled studies in pregnant women" to address the issue of potential fetal risk. Therefore, omeprazole should remain classified as a "Pregnancy category C" drug which means that animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

Though the epidemiological studies are not adequate to fully address the safety concerns of omeprazole use in pregnancy, the consultant reviewers generally felt that these cohort studies were generally well-conducted and provided reassuring information that omeprazole did not appear to increase either spontaneous abortions or congenital malformations. The consultants felt strongly that larger prospective studies would not likely give meaningfully better information and were likely to be too resource intensive to be feasible.

Because omeprazole is on occasion used in women during pregnancy (intentionally or inadvertently), I think it is reasonable to include some information from these reasonably well-done epidemiology studies in the labeling. The following modifications should be made to the

sponsor's requested labeling for the Precautions: Pregnancy Omeprazole section of the labeling:

1. "There are no adequate and well-controlled studies in pregnant women". [Note: The word "or" is revised to "and", as per 21CFR 201.57(f)(6)(i)(c)].

2. The sponsor has proposed the following wording of a new subsection:

a.

b.

c. [redacted]

Also, changes as recommended by FDA Pharmacologist's Review dated 10/26/00 should be made to the labeling.

cc:
NDA 19-810
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-180/HGallo-Torres
HFD-180/MWalsh
HFD-180/JChoudary
HFD-180/LZhou

# APPENDIX

**Comments on the design characteristics and feasibility of a large, prospectively designed epidemiological study of women exposed to Omeprazole during pregnancy**

Since some of the issues of concern regarding use of Omeprazole during pregnancy relate to spontaneous abortion and congenital heart defects among offspring, desirable design characteristics of a prospective cohort study to address these issues include:

- Determination of the minimum excess risk that would be of clinical and public health importance to detect.

- Estimation of early pregnancy losses.

- Estimation of size of cohort study to detect the minimum excess risk for spontaneous abortions, and for malformations accounting for early pregnancy losses. The following numbers provide a rough idea of the kind of sample sizes needed per cohort of exposed and unexposed pregnancies to detect a minimum relative risk for one of the more common major congenital heart defects (i.e., ventricular septal defects) with a baseline prevalence of about 1 per 1000:

| Minimum RR | N per exposure group |
|---|---|
| 2 | 4300 |
| 3 | 1500 |
| 4 | 800 |
| 5 | 560 |

For other heart defects, with a much lower prevalence, the sample sizes would have to be much greater.

- Enrollment of a large cohort of women planning a pregnancy or who have just become pregnant.

- A substantial number of such women end up using Omeprazole during the first trimester of pregnancy

- Baseline and regularly scheduled interviews and examinations of all women in the cohort are conducted to ascertain

    - Pregnancy status
    - Use of Omeprazole
    - Use of other prescription and nonprescription drugs
    - Use of alcohol and cigarette smoking
    - Use of vitamin supplements
    - Illnesses during the first trimester

- Follow-up of all women to ascertain, evaluate, and validate all pregnancy outcomes, using standardized procedures.

- Create and manage, on an ongoing basis, a complex database.

- Conduct timely evaluations of safety issues.

/s/
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Kathy Robie-Suh
2/7/01 03:05:42 PM
MEDICAL OFFICER

Hugo Gallo Torres
2/7/01 04:56:32 PM
MEDICAL OFFICER

Lilia Talarico
2/7/01 05:21:42 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

| | |
|---|---|
| NDA: | NDA 19-810 (SE8-058) |
| Sponsor: | Astra Merck, Inc. |
| Drug name: | Prilosec (omeprazole) Delayed-Release Capsules |
| Date submitted: | October 7, 1998 |
| Date Received: | October 7,1998 |
| Review completed: | January 21, 1999 |
| Reviewer: | Kathy M. Robie-Suh, M.D., Ph.D. |

**Background:**
Omeprazole was approved in 1989 for treatment of severe erosive esophagitis, poorly responsive gastroesophageal reflux disease (GERD) and pathological hypersecretory syndromes. Since introduction of omeprazole, the list of indications has been broadened to include symptomatic GERD, healing and maintenance of erosive esophagitis, and healing of benign gastric and duodenal ulcers. Because animal studies in rats and rabbits showed fetal toxicity, the drug is classified as Pregnancy category C. The sponsor has submitted this supplement to request a change in the pregnancy classification of the drug to Pregnancy category B and to support revisions to the **Precautions** section of the Prilosec labeling.

The sponsor has collaborated with three independent groups in Sweden, Canada, and the United Kingdom and Italy to conduct epidemiological studies of the use of omeprazole during pregnancy. Reports of these studies are included in this submission. Also, the sponsor has provided a summary of the spontaneous marketing reports from the post-marketing safety database. The sponsor estimates that about million treatment courses of omeprazole have been dispensed worldwide.

**Proposed Labeling Changes:**
The proposed changes to the omeprazole labeling are listed below.
Under **Precautions**: *Carcinogenesis, Mutagenesis, Impairment of Fertility* the sponsor proposes the following changes:

- Revise the last part of the first sentence of the first paragraph from "(approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg)" to "0.7 to times a human dose of 20 mg/day, as expressed on a body surface area basis)".

- Revise the fourth sentence of the first paragraph from "In one of these studies female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, ..." to "In one of these studies female rats were treated with 13.8 mg omeprazole/kg/day a human dose of 20 mg/day, based on body surface area) for one year,..."

- "A mouse micronucleus test at 625 and 6250 times the human dose.

- "A second mouse micronucleus study at 2000 times the human dose ...."

- Delete the last sentence of the section which says: "In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals." And add: "Omeprazole at oral doses up to mg/kg/day times a human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats."

Under **Precautions:** *Pregnancy* the sponsor proposes the following changes:

- Change *"Pregnancy Category C"* to *"Pregnancy Category B"*.

- of this section from:

"Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 time the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.
In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo lethality, fetal resorbtions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose)."

to:

- Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy"

- "Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus".

Under **Precautions:** *Nursing Mothers* the sponsor proposes the following changes:

- Revise the first two sentences from "It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups."
  to: "Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200ml of milk."

- Revise the third sentence from "Because many drugs are excreted in human milk,..." to "Because omeprazole is excreted in human milk,..."

**Materials Submitted:**
This submission consists of 18 volumes containing the following:

- Vol. 1-1 — Index, Summary of Application including proposed text of labeling (annotated and non-annotated)
- Vols. 1.2 through 1.9 — Nonclinical Pharmacology and Toxicology Section
- Vols. 1.10 through 1.18 — Clinical Data Section

For this review I have evaluated the clinical information submitted in the supplement application.

**Summary of Nonclinical Information:**
The nonclinical pharmacology and toxicology information is being reviewed by FDA Pharmacology. However, below I have briefly summarized this information.

In oral fertility studies (omeprazole doses up to 320mg/kg) and intravenous fertility studies (omeprazole doses up to 100mg/kg) in rats, the sponsor found no adverse effects on fertility. The sponsor found no evidence of teratogenicity or other adverse embryo-fetal effects following oral administration of omeprazole at doses up to 138 or 320 mg/kg/day in pregnant rats. Following intravenous injection of omeprazole, no adverse embryo-fetal effects were seen at doses up to 100mg/kg/day. In rabbits, the sponsor found significantly increased fetal loss at doses of 69.1mg/kg and above, but no evidence of teratogenicity. (In rabbits these doses showed severe maternal toxicity and the sponsor attributes the fetal loss to poor maternal condition. Omeprazole up to 32mg/kg given intravenously in rabbits did not show embryo-fetal effects. In peri- postnatal studies, oral administration of omeprazole at doses up to 320mg/kg and intravenous doses up to 100mg/kg did not result in differences between control and omeprazole groups in gestation length, delivery index or number of live-born offspring. There was a slight decrease in body weight gain in the offspring during the lactation period concurrent with decreases in maternal body weight gain and food consumption. The no adverse effect level for this effect was 43.1mg/kg. No differences in physical development, behavioral or learning ability in the offspring were detected.

In mice, rats and sheep omeprazole readily crossed the placenta achieving similar blood levels in mother and fetus. Omeprazole is found in the milk of lactating rats.

The usual oral therapeutic dose of omeprazole in humans is 20mg daily, which equals 14mg/m$^2$, expressed on a body surface area basis for a 50 kg person. Based on this body surface area, a dose of 69.1mg/kg is about 40 times the usual human dose and a dose of 43.1mg/kg is about 19 times the usual human dose.

The sponsor concludes that the studies do not indicate any adverse effects of omeprazole on fertility or any teratogenic potential of omeprazole and

**Summary of Clinical Information Submitted:**
The clinical information submitted consists of:

- 3 clinical epidemiological studies,
- surveillance data from the sponsor's spontaneous reporting system and
- a review of the published literature on the use of omeprazole during pregnancy.

This information is described and discussed below.

*Clinical Epidemiological Studies:*

I. **Title:** United Kingdom and Italy Epidemiology Study: Use of Cimetidine, Omeprazole, and Ranitidine in Pregnant Women and Pregnancy Outcomes. [Investigators: A Ruigomez, LA Garcia Rodriguez, C Cattaruzzi, MG Troncon, L Agostinis, M-A Wallander and S Johansson]. (NDA Vol. 142.10 through 142.15)

*Description of Study:* This study proposed to examine the cumulative incidence rate of spontaneous and voluntary abortions and major congenital malformation in pregnant women taking cimetidine, omeprazole and/or ranitidine and compare it to the rates in women not exposed to acid-suppressing drugs during pregnancy.

The database used consisted of the U.K. General Practice Research Database (GPRD) and a birth registry and prescription database from the region in northeastern Italy. The U.K. GPRD involved about 441 practices and about 3 million patients in the U.K. Information collected on patients in this database included demographics, details of general practitioner's consultations, notes of specialist referral and hospital admissions, laboratory test results and sometimes additional information. Prescriptions and the indication and patient diagnoses are included. This computerized database was started by a commercial company in the 1980s and has since 1994 belonged to the U.K. Department of Health and been maintained by the Office of National Statistics. The database has been used most frequently for studies of drug safety, such as epidemiology of drug-induced liver injury and evaluation of association of venous thromboembolism and hormone replacement therapy. For this study data collected between January 1991 and October 1996 were used. The Italian birth registry database was started in 1989 and served a region with 1.2 million inhabitants.

For inclusion in the study cohort women must have been younger than 45 years old and have a code for pregnancy between January 1991 and October 1996 (U.K.) or younger than 45 years old and had a hospital delivery between January 1991 and December 1996 (Italy). Dates of last menstrual period and outcome of pregnancy and date were collected and live birth babies were linked to the respective mothers. All women who received a prescription for cimetidine, omeprazole or ranitidine during the first trimester of pregnancy were identified. (Women who had received more than one acid-reducing drug were excluded). Pregnancy loss at 28 weeks of gestation or later were classified as stillbirth. Termination of pregnancy due to prenatal diagnosis of malformation was considered a stillbirth. Live-births or stillbirths with a structural defect of unknown cause detected prenatally, at birth or within the first year of life were

classified as congenital malformations. (Birth defects/malformations known to be of genetic origin (chromosomal and genic syndromes) were not included). Malformation prevalence rates were calculated for each drug using the number of offsprings as denominator.

*Results:* Outcomes for exposed and non-exposed women in both the datasets are summarized in the following table:

**Pregnancy Outcomes in Women Receiving Acid-Suppressing Drugs During First Trimester of Pregnancy**

| | U.K. | | Italy | | Total | |
|---|---|---|---|---|---|---|
| | Exposed (omeprazole/ranitidine/cimetidine) | Non-Exposed | Exposed (omeprazole/ranitidine/cimetidine) | Non-Exposed | Exposed (omeprazole/ranitidine/cimetidine) | Non-Exposed |
| Total Pregnancies | 97/224/223 | 635 | 37/98/10 | 912 | 134/322/233 | 1547 |
| Offsprings<br>Stillbirths<br>Livebirths | 100/229/227<br>--/2/3<br>100/227/224 | 651<br>12<br>639 | 39/101/10<br>--/--/--<br>39/101/10 | 924<br>3<br>921 | 139/330/237<br>--/2/3<br>139/328/234 | 1575<br>15<br>1560 |
| Malformed offsprings | 5/17/9 | 37 | --/3/2 | 27 | 5/20/11 | 64 |
| Preterm offspring (<37 weeks) | 7/23/14 | 48 | 4/6/-- | 67 | 11/29/14 | 115 |

reviewer's original table, based on sponsor's tables NDA Vol. 142.10, pp. 8-001-017 and 8-001-018

The study identified 1179 pregnancies from the U.K. General Practice Research Database and 1057 from the ✓ ✓
Spontaneous abortions, voluntary abortions and ectopic pregnancies were not included in the study cohort. There were 34 twin pregnancies (21 U.K., 13 Italy) and 5 triplet pregnancies (3 U.K.; 2 Italy). There were 20 stillbirths and 2261 live-births in this study. The congenital malformation rates were: cimetidine, 11/233 (4.7%); omeprazole, 5/134 (3.7%); ranitidine, 20/322 (6.2%) and non-exposed 4.1% (64/1547). The sponsor found no differences between the treatment groups in the risk for malformations. Malformations according to first trimester exposure are shown in the following table:

**Distribution of Malformations According to First Trimester Exposure in the UK- Italy Epidemiology Study**

| Malformation | Omeprazole (N=139) | Ranitidine (N=328) | Cimetidine (N=234) | Non-Exposed (N=1560) |
|---|---|---|---|---|
| Central Nervous system | | | | |
| Spina bifida/hydrocephaly | | 1 | | 1 |
| Frontal atrophy/retinal dystrophy | | | | 1 |
| Cranio-Orofacial | | | | |
| Cleft lip with cleft palate | | | 1 | 1 |
| Cleft palate only | | 1 | | 1 |
| Asymmetrical skull/plagiocephaly | | 1 | | 5 |
| Accessory auricle/preauricular fistula | | | | 2 |
| Tongue tie | 1 | 1 | | 4 |
| Eye | | | | |
| Aniridia | | | | 1 |
| Duane's eye syndrome | | 1 | | 1 |
| Cardiac | | | | |
| Cardiac septal defects | 2 | 1 | | 3 |
| Malformed cardiac chambers/connect | | | | 1 |
| Abnormalities of cardiac valves | | 1 | | 3 |
| Musculoskeletal | | | | |
| Accessory fingers/polydactyly | | | 1 | 4 |
| Syndactyly | | 1 | | |
| Dysplastic hip/dislocation/clicking hip | 1 | 3 | 3 | 6 |
| Sacral sinus | | 1 | | |
| Talipes varus | | | | 3 |
| Genital and Urinary | | | | |
| Hypospadias | | | 2 | 1 |
| Testes undescended | | 2 | | 9 |
| Congenital hydrocele/inguinal hernia* | 1 | 2 | 1 | 4 |
| Ovarian cyst | | 1 | 1 | 1 |
| Renal defects/hydronephrosis | | | 1 | 2 |
| Potters syndrome (bilateral renal agenesis) | | | | 1 |
| Gastrointestinal | | | | 2 |
| Pyloric stenosis | | | 1 | |
| Polymalformation | | | | |
| Multiple skeletal abnormalities | | | | 1 |
| Pyloric stenosis and talipes equinovarus | | 1 | | |
| Cleft palate and lip and auricle abnormalities | | | | 1 |
| Polydactyly and undescended testicle | | | | 1 |
| Genetic Abnormalities | | | | |
| Hallerman Streiff syndrome | | 1 | | |
| Pradder Willy syndrome | | | | 2 |
| Down's syndrome | | 1 | | |
| Monosomy 18p | | | | 1 |
| Anomaly chromosomes 10 and 12 | | | | 1 |
| TOTAL | 5 | 20 | 11 | 64 |

n= number of women with first trimester exposure
* One case also had a genetic disorder (neurofibromatosis)

sponsor's table slightly modified, NDA Vol. 142.1, pp. 3-001-071 and 3-001-072

Malformations seen among the offspring of women prescribed omeprazole included: cardiac septal defects (2), tongue tie (1), congenital hydrocele/inguinal hernia (1), and dysplastic hip/dislocation/clicking hip (1). The most frequently seen malformations in the non-exposed patients were: undescended testes (9), dysplastic hip/dislocation/clicking hip (6), asymmetrical skull/plagiocephaly (5), accessory auricle/preauricular fistula (4), accessory fingers/polydactyly (4), and congenital hydrocele/inguinal hernia (4).

*Reviewer's comments:* The study appears not to have been conducted as thoroughly as intended in the protocol. For instance the protocol indicated that women "younger

than 45 years at date of pregnancy code and having received a prescription for one of the three study drugs anytime from 180 days before date of pregnancy code until 180 days after" would be identified, that records would be examined to identify case of spontaneous abortion and that the drug groups would be divided into early exposure (first and/or second trimester) and late exposure (third trimester).

This study was not designed to prospectively examine effects of omeprazole during pregnancy. Minimal information was collected about each of the pregnancies. There is no information as to doses of omeprazole prescribed, whether the women actually took any of the prescription, or duration of time the medication was taken. The study did not examine the database with regard to occurrence of spontaneous abortions. Effects of omeprazole use during second and/or third trimesters of pregnancy was not examined. This study does not contribute significantly to evaluating the fetal effects of omeprazole use during pregnancy. The number of women exposed in this study is fairly small, including only 134 women possibly exposed to omeprazole during first trimester of pregnancy; therefore, only events occurring at a frequency of at least 7 in 1000 pregnancies would be reasonably likely to be observed in this dataset.

II. **Title:** Sweden Epidemiology Study: Delivery Outcome after the Use of Acid-suppressive Drugs in Early Pregnancy with Special Reference to Omeprazole [manuscript by B Kallen, M.D.] (NDA Vol. 142.16)

*Description of Study:* This was a retrospective cohort study intended to examine delivery outcome after maternal use of acid-suppressing drugs during early pregnancy. The database used was women in the Swedish Medical Birth Registry giving birth from 1995 through early 1997. Maternal drug use was identified by patient interview. Outcome measures assessed included presence of congenital malformations, gestational duration, birth weight, body length, head circumference, low Apgar score at 5 minutes and infant survival. Congenital malformations were further explored by linkage with the Register of Congenital Malformations.

*Results:* A total of 547 women (with 553 offspring) using acid-suppressing drugs were identified (out of a total of about 200,000 births). The drugs used were: omeprazole, 262; lansoprazole, 13; cimetidine, 35; ranitidine, 156; famotidine, 58; nizatidine, 3; cimetidine+famotidine, 1; ranitidine+famotidine, 2; omeprazole+cimetidine, 2; omeprazole+ranitidine, 18; and misoprostol, 3. In many of these patients there was concurrent use of other medications such as analgesics, antacids, antibiotics, antiasthmatics, antihistamines and others. This group of women tended to be older, had an increased proportion of first pregnancies and had somewhat more smokers (22%) as compared to non-exposed mothers (16%).

A total of 19 malformed infants were identified [2 were reported only in the Register of Congenital Malformations data]: 10 exposed to proton pump inhibitors, 8 to $H_2$-receptor antagonists and 1 to both types of drugs). This was a congenital malformation rate of 3.4% among these births as compared to a crude malformation rate of 3.9% in the Medical Birth Registry. There do not appear to have been more than one congenital malformation in any infant. The malformations found are summarized in the following table:

**Infants Identified with Congenital Malformations According to Acid-Suppressive Drugs Used**

| Malformation | Omeprazole (N=262) | Lansoprazole (N=13) | Ranitidine (N=156) | Cimetidine (N=35) | Omeprazole + Ranitidine (N=18) | Total (N=553)[@] |
|---|---|---|---|---|---|---|
| Encephalocele | | | | 1[a] | | 1 |
| Cerebral AV[*] malformation | | | 1[a] | | | 1 |
| Ventricular septal defect | 3 | | | | | 3[b] |
| Atrial septal defect | | 1 | | | | 1 |
| Patent ductus arteriosus | 1 | | | | | 1 |
| Unspecified cardiac defect | 1 | | 1 | | | 2 |
| Hydronephrosis | | | 1 | | | 1 |
| Undescended testicle | | 1 | 1 | | | 2 |
| Urethral valve | 1 | | | | | 1 |
| Hypospadias | | | 1 | | | 2 |
| Facial anomaly | 1 | | | | | 1[c] |
| Unstable hip | | | 1 | 1 | 1 | 2 |
| Down syndrome | 1 | | | | | 1 |
| Total | 8 | 2 | 6 | 2 | 1 | 19 |

[@] N=number of births; Note: Total N includes, in addition to infants exposed to the listed drugs, a total of 69 patients who were exposed to famotidine (58), nizatidine (3), cimetidine+famotidine (1), ranitidine+famotidine (2), omeprazole+cimetidine (2), or misoprostol (3). There were no malformations among these infants.

[*] AV = arterio-venous

[a] from Register of Congenital Malformations, (not listed in the birth registry data). One with prenatal exposure to cimetidine had a large encephalocele (resulting in death during the first day of life) and one with pre-natal exposure to ranitidine had non-immune hydrops and a cerebral arterio-venous malformation (died at 1 day old).

[b] In the sponsor's table the total is 4 cases of ventricular septal defect, but this is not consistent with the listing.

[c] In the sponsor's table the total is 2 cases of facial anomaly, but this is not consistent with the listing.

sponsor's table modified, NDA Vol. 142.16, p. 8-007-023

In this study there were 282 omeprazole exposures and 9 cases of congenital malformations of these [8 cases with omeprazole alone; 1 case with omeprazole+ranitidine]. [Information about number of exposures to the other listed drugs is not given]. The sponsor found no statistically significant difference between malformation rates between the malformation rates with either of these drugs and the overall malformation rate in the Medical Birth Registry database. The sponsor indicates that in order to verify a 25% increased risk for any congenital malformation (alpha = 0.05; beta = 0.080), data on 3,300 exposures would be needed (about 20 more years of data from this database assuming unchanging exposure rate). No information about time of exposure or duration of exposure is given. The report does not discuss any of the other endpoints such as APGAR score or gestational duration.

*Reviewer's comments:* This study is not particularly useful in evaluating possible fetal/embryo toxicity of omeprazole. No doses or durations of exposure to omeprazole were recorded. Rates of spontaneous abortions/miscarriages were not assessed.

**III.** **Title:** Motherisk (Canada) Epidemiology Study: A Preliminary Report on the Safety of Omeprazole During Pregnancy [Investigators: A Lalkin, R Loebstein, A Addis, F Ramezani-Namin, P Mastroiacovo, T Mazzone, T Vial, M Bonati, and G Koren] (NDA Vol. 142.17)

*Description of Study:* This was a multi-center, prospective, controlled study looking at the incidence of congenital malformations in women exposed to omeprazole during pregnancy as compared to women exposed to non-teratogens (NTC) and disease-

paired controls who used H2-blockers for similar indications (DPC). Primary endpoint was occurrence of major congenital malformations. Secondary endpoints were pregnancy outcome, birth weight, rate of preterm delivery, gestational age at delivery, and neonatal health problems. The study population consisted of all pregnant women exposed to omeprazole and counseled since its introduction into Canada by the Motherisk team at the Hospital for Sick Children in Toronto. Also, included were omeprazole exposures from the Telefono Rosso (Rome) database, the Service de Pharmaco-Toxicovigilance (Lyon) database, and the Centro Regionale d'Informazione sul Farmaco (CRIF- Milan) database. The comparator group women (NTC and DPC) all were from the Toronto, Canada database.

*Results*: A total of 113 women exposed to omeprazole during pregnancy were followed (59 Toronto; 34 Rome; 13 Lyon; 7 Milan). Mean age was 31.5 years, mean gravidity, 2.3; parity, 0.8; non-smoking, 83%; no alcohol, 90%. There was concurrent use of anti-peptic medications and/or "pro-kintetics" ($H_2$-blockers, antacids, sucralfate, bismuth subsalicylate, Tums, cisapride) in 37% of these patients. The sponsor states that demographic features at the different sites were comparable; however, these data are not provided by center. Of the 113 women identified, 101 (89%) reported exposure during the first trimester. Only 15% reported omeprazole use throughout pregnancy. Pregnancy outcome results are summarized in the sponsor's table below:

**Pregnancy Outcome of Women Exposed to Omeprazole during Pregnancy Compared to Disease-Paired Controls (DPC) and Non-Teratogen Controls (NTC)**

| Characteristics | Omeprazole (N=113) | DPC ($H_2$blockers) (N=113) | NTC (N=113) |
|---|---|---|---|
| Live birth (5)<br>Spontaneous abortion<br>Therapeutic abortion | 91/113 (81%)<br>16/113 (14%)<br>6/113 ( 5%) | 101/113 (89%)<br>9/113 ( 8%)<br>3/113 ( 3%) | 99/113 (88%)<br>9/113 ( 8%)<br>5/113 ( 4%) |
| Major malformations per live births (Exposure 1st trimester only)(%) | 4[a]/78 ( 5.1%) | 3[b]/98 ( 3.1%) | 2[c]/66 ( 3.0%) |
| Gestational age (wk) | 39.1 | 38.7 | 39.3 |
| Preterm (<37 wk) | 8/84 ( 9.5%) | 16/101 (15.8%) | 8/99 ( 8.1%) |
| Cesarian section | 18/91 (19.7%) | 19/101 (18.8%) | 20/99 (20.2%) |
| Birthweight (g) | 3325 | 3397 | 3403 |

[a] included one case each of ventricular septal defect, polycystic kidneys, uretero-pelvic stenosis and patent ductus arteriosus
[b] included 2 cases of ventricular septal defect and on case of atrial septal defect
[c] included 1 case of atrial septal defect with pulmonary stenosis and 1 case of developmental delay

sponsor's table, modified, NDA Vol. 142.17, p. 8-008-018 of study manuscript

Rates of major malformations were 4% in the omeprazole group, 2% in the non-teratogen exposed group, and 2.8% in disease-paired controls. No differences between groups were statistically significant. Also, the sponsor found no significant differences among the groups in any of the secondary endpoints.

Rates of spontaneously occurring abortions were 14% in the omeprazole group, 8% in the disease-paired controls, and 8% in the non-teratogen treated group (sponsor's p-value=0.2).

*Reviewer's comments:* This study did not show any clear evidence of adverse effects of omeprazole during pregnancy. There was a numerically higher rate of spontaneous abortions in the omeprazole-treated group as compared to both control groups. Rates

of major malformations were similar among the three groups. The data were not examined by omeprazole dose and/or duration of treatment.

*Spontaneous Post-Marketing Reports:*
The sponsor obtained estimates for worldwide patient treatment with omeprazole from the IMS MIDAS database which is a multinational, integrated database of information about sales volumes and prescriptions in about 70 countries from 1993 to March, 1998. Based on this database about million patient treatments/prescriptions for omeprazole capsules (about per prescription) have been dispensed. For all forms of omeprazole there have been an estimated million patient treatments/prescriptions (average units per prescription) worldwide.

The sponsor estimated use of omeprazole in pregnancy at about courses of therapy. This estimate was based on the data from the Swedish national registry of pregnancies and the IMS prescription database. From 1994-1996 there were about 200,000 pregnancies registered, which had used omeprazole during pregnancy. Extrapolating these data the sponsor calculated that of the estimated worldwide use of about million courses of omeprazole, about of these exposures would have been in pregnant women.

The sponsor's spontaneous report database contains reports of 47 cases of some fetal abnormality and 36 cases of normal fetal outcome in women exposed to omeprazole during pregnancy. The most frequent abnormalities were: anencephaly (4 cases), general heart defects (3 cases). The sponsor cites the incidence of anencephaly and heart malformations in the general population as 8-9 per 1,000 live births and 1 to 3.5 per 1,000 live births, respectively and concludes that the reported cases do not indicate an increased incidence of these abnormalities in pregnant women exposed to omeprazole. The database contains 6 reports of fetal death during first trimester, 3 fetal deaths during second trimester, 3 stillbirths (after 28 weeks gestation), 3 fetal deaths gestational age unspecified and 1 ectopic pregnancy. There were 4 cases of elective abortion and 1 case of abortion following omeprazole overdose and "psychiatric problems"; neither of these had fetal malformations.

The database also contains 8 reports of malformations in infants born to mothers who received one or two doses of omeprazole in a European study of omeprazole for treatment of aspiration prophylaxis in patients undergoing elective Caesarian-section. [Note: The total number of pregnant women entered in this study is not reported].

*Published Literature:*
The sponsor's literature search revealed three publications which contained information regarding use of omeprazole during pregnancy. One publication (Brunner, G et al. Gastroenterol. 112 (4 Suppl): A79 (1997)) summarized the results of 9 pregnancies during which the mothers used omeprazole (6 at conception, 2 late in pregnancy,1 intravenous omeprazole followed by oral omeprazole). In 4 of the cases omeprazole (20 mg or 40 mg daily) was used throughout the pregnancy. There were no malformations in the offspring of any of these pregnancies.

Another publication (Choulika, S et al. Therapie 52:612 (1997)) reported 25 cases involving proton pump inhibitors administration during pregnancy (most during the period of

organogenesis, 14 to 58 days). Twenty-three of these cases involved omeprazole, however, particular drug is not identified for the individual outcomes. Most of the cases had concomitant use of other drugs such as antacids, H2-receptor antagonists, antiemetics, antidepressants, antibiotics, and antiinflammatories. There were 2 spontaneous abortions (5 wks and 10 wks) and 2 elective abortions. Outcome was unknown for 1 pregnancy. Twenty pregnancies resulted in live births. One baby had a cavernous hemangioma and another was premature with low birth weight.

There was a report of one case where a woman with GERD used ranitidine and cisapride early in her pregnancy and used omeprazole during the last trimester and post-partum. She gave birth to a healthy infant at 36 weeks gestation. The breast milk was assayed for omeprazole which was found with a peak concentration of ( ) which was about 7% of the mother's peak serum concentration. The authors estimated that this would translate to a maximum omeprazole ingestion of 4ug per 200ml of breast milk and that in addition this unprotected omeprazole would likely be destroyed in the infant's stomach.

There were, in addition, several studies of use of omeprazole just prior to cesarean section. Use in these patients was very brief and late in pregnancy so these reports were not discussed further. Also, there were some case studies which were included in the sponsor's spontaneous report database.

**Reviewer's Comments:**
Currently omeprazole is classified as a "Pregnancy category C" drug which means that animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Because animal studies of omeprazole have shown adverse effects on the fetus, the sponsor must provide "adequate and well-controlled studies in pregnant women" which "fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no risk in later trimesters)" in order to change the classification to "Pregnancy category B". The information in this submission does not meet that requirement.

The sponsor has submitted 3 epidemiologic studies, two of which are retrospective. The reports give little or no information about dose and/or duration of omeprazole therapy, compliance and concomitant medications. These studies are inadequate to evaluate the effect of administration of therapeutic courses of omeprazole during pregnancy. While in most instances mothers indeed gave birth to apparently normal infants, the studies were not designed to allow reliable assessment of relationship between omeprazole administration and pregnancy outcome. While these studies and the spontaneous report data and literature search do not point to any clear association of omeprazole with fetal malformations or spontaneous abortions, the material provided does not constitute an adequate basis for evaluating fetal risk from omeprazole exposure during pregnancy.

**Conclusions and Recommendations:**
The sponsor has not provided adequate information to evaluate fetal risk from omeprazole exposure during pregnancy. I recommend that the Pregnancy Category C classification for omeprazole remain unchanged and that the product label not be modified at this time.

To support a change in the Pregnancy Category C classification to Pregnancy Category B the sponsor should plan a prospective, controlled study of omeprazole in women having a serious medical need for the drug during pregnancy.

Kathy M. Robie-Suh, M.D., Ph.D.

cc:
NDA 19-810
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-180/HGallo-Torres
HFD-180/MWalsh
HFD-180/JChoudary
HFD-180/EDuffy
f/t 1/21/99 jgw
N/19810901.0KR

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-810/S-003 & S-058

# PHARMACOLOGY REVIEW

**MEMORANDUM**

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

DATE: September 29, 2003

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 19810 (PRILOSEC) Supplement # S-003 & S-058- sNDA Amendment Dated April 03, 2003- Revised Draft Labeling

TO: NDA 19810

In response to the Division's approvable letter dated January 31, 2003, the sponsor in the above cited amendment submitted the revisions under PRECAUTIONS, 1) Carcinogenicity, Mutagenicity, Impairment of Fertility, 2) Pregnancy, Omeprazole, Pregnancy Category C and 3) Nursing Mothers. Sponsor's revisions under each subsection are reviewed below.

1) Carcinogenicity, Mutagenicity, Impairment of Fertility: Sponsor accepted Agency's text from the approvable letter of 1/31/03 for most of this subsection with the exception of alternate wording proposed for the incidence of brain astrocytomas observed in the 52-week toxicity study in rats. In the sponsor's alternate text, reference is made to the findings in the two-year rat carcinogenicity study submitted in the original NDA. On further examination of the original NDA, It is the conclusion of the undersigned that the sponsor's alternate text for this portion is acceptable.
2) Pregnancy, Omeprazole, Pregnancy Category C: Sponsor accepted all the changes in the approvable letter with the exception of the spelling error on page 23 of the submission. In the second paragraph, "pregnant rabbits " is shown as "pregnancy rabbits". Sponsor should be asked to rectify this error.
3) Nursing Mothers: The sponsor did not make any changes suggested in the approvable letter, which relates to the observed presence of omeprazole in the breast milk of a woman following treatment. Sponsor should be asked to rectify this omission.

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

Cc:
NDA
HFD-180

HFD-181/CSO
HFD-180/Dr. Choudary

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/s/

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Jasti Choudary
9/29/03 10:10:37 AM
PHARMACOLOGIST

MEMORANDUM

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

DATE: December 13, 2002

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 19810(Prilosec Delayed Release Capsules)—Resubmission Dated July 31, 2002 to Supplement # 058(SLR-003-BL; SE 8-058-BL)—Labeling Revisions

TO: NDA 19810

In the Division's approvable letter dated February 7, 2001, the sponsor was advised to incorporate changes to labeling under PRECAUTIONS, Carcinogenicity, Mutagenicity, Impairment of Fertility

Sprague –Dawley rats in a dose related manner. The statement is as follows: "In a 52-week toxicity study

Sponsor in their submission dated August 16, 2001 In the review dated February 1, 2002, it was recommended that that the statement should be . In a Telecon dated February 12, 2002, the sponsor (Dr. Horowitz) asked the Regulatory Project Manager Ms. Walsh

After consultation with the undersigned, MS. Walsh advised the sponsor to provide tumor data in age matched animals of the same strain in the same testing laboratory around the time the study was conducted.

In the present submission, sponsor provided their response. It consisted (1) a translated Japanese published report of chronic toxicity study in tats conducted by a different organization during the period of June 1988 to March 1990 and (2) a translated 1999 Japanese publication dealing with data of two year carcinogenicity studies. The 52-week chronic toxicity study of omeprazole (Report # 63-067) was conducted by during the period of September 1986 to July 1988 and the incidences of brain astrocytoma were 4.3% to 8.3%in the treated male rats with none in the concurrent control male rats. The information on the chronic toxicity study provided by the sponsor is not from the same testing laboratory and as such does not represent the historical incidences in the testing laboratory and the period of the study (June 1988 to March 1990) also does not correspond to the time of the omeprazole toxicity study (September 1986 to July 1988). The background information from the two-year carcinogenicity studies during the period of 1996 to 1999 are not

relevant to the findings in the 52-week chronic toxicity study of omeprazole. Nevertheless, the 3.6% background incidence of this report is well below the 4.3% to 8.3% incidence rates of omeprazole toxicity study.

Recommendation: The information provided by the sponsor does not satisfy the recommended historical control incidence data.

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

Cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary

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/s/

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Jasti Choudary
12/13/02 11:47:00 AM
PHARMACOLOGIST

FEB 1 2002

MEMORANDUM

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

DATE: February 1, 2002

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 19810 (Prilosec Delayed Release Capsules) Supplement # 058 Dated August 16, 2001- Labeling Revisions

TO: NDA 19,810

In the submiission dated August 16, 2001, the sponsor provided response to Division's letter dated February 7, 2001. In the Division's letter, the sponsor was asked to submit a final printed labeling with recommended revisions. Instead, the sponsor provided a revised draft labeling . Ms. Walsh in her RPM review dated January 24, 2002 recommended that sponsor's revisions under " PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility " should be reviewed by Pharmacology. Sponsor's revisions are addressed below.

. Historically in this strain of rat , there is no background incidence in one-year toxicity study. Negative findings in the mouse tests have no bearing on the findings in the rat toxicology study. In the two-year carcinogenicity study, 50 animals/group is still a small sample and a negative finding in such a study is no reason to eliminate the positive findings in a study of shorter duration. A gastric adenocarcinoma occurred in second rat carcinogenicity study of omeprazole in which animals were treated only for one year while such tumors were not observed in animals treated for two years. This finding was included in the labeling with a qualifying statement.

Sponsor may be given the option of adding a qualifying statement. The other changes in this portion are acceptable.

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

Cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary

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/s/

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Jasti Choudary
2/1/02 03:34:14 PM
PHARMACOLOGIST

Walsh -

NDA 19,810

OCT 26 2000

# PHARMACOLOGIST'S REVIEW OF NDA 19,810
## (Supplement SE8-058-A2 Dated August 4, 2000)

**Sponsor (or agent):** AstraZeneca LP
Wayne, PA
**Manufacturer for drug substance:** Same

**Reviewer Name:** Timothy W. Robison, Ph.D.
**Division Name:** Gastrointestinal and Coagulation Drug Products
**HFD#** 180

**NDA number:** 19,810
**Serial number/date/type of submission:** Supplement dated August 4, 2000
**Date of HFD-180 Receipt:** August 7, 2000
**Review Completion Date:** October 24, 2000
**Information to sponsor: Yes ( ) No (X)**

**Drug:**
**Generic Name:** Omeprazole
**Trade Name:** Prilosec®

**Drug Class:** Gastric parietal cell $H^+,K^+$-ATPase inhibitor/Proton Pump Inhibitor

**Introduction and drug history:** Omeprazole (Prilosec®) has been marketed as a prescription drug for short-term treatment of active duodenal ulcer, treatment of gastroesophageal reflux disease (GERD), treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis). In NDA 19,810 Supplement #SE8-058 dated October 7, 1998, the sponsor submitted additional preclinical and clinical studies with the intention of providing support for a change in the Pregnancy Category Label from C to B. In a letter from the Division to the sponsor dated October 7, 1999, this information was determined to be inadequate and the supplemental application was not approvable. Thus, omeprazole remained under Pregnancy Category C.

**Studies reviewed within this submission:** The sponsor has proposed changes in product labeling based upon studies submitted in Supplement #SE8-058 dated October 7, 1998. Current product labeling is listed below followed by the sponsor's proposed labeling within quotations. The sponsor's proposed labeling is evaluated followed by a recommended version if necessary.

**1. Carcinogenesis, Mutagenesis, Impairment of Fertility:**

**Current Labeling:**

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

**Sponsor's Version:**

"In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (0.7 to times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is

difficult to interpret.

Omeprazole at oral doses up to [redacted] was found to have no effect on fertility and reproductive performance [redacted]

**Evaluation:**

The dose of 140.8 mg/kg/day administered to rats is 57 times the human dose of 20 mg/day.

The unidentified tumor in the stomach of 1 rat was subsequently determined to be a poorly differentiated adenocarcinoma.

In a 52-week oral toxicology study, Sprague-Dawley rats received omeprazole at doses of 0, 0.4, 2, and 16 mg/kg/day. For the brain, astrocytomas were observed for male rats at 0.4, 2, and 16 mg/kg/day with an incidence of 1 of 23 (4.3%), 1 of 23 (4.3%), and 2 of 24 (8.3%), respectively. There was no reported spontaneous incidence rate for brain astrocytoma in 12-13 month studies [redacted] Bronchiolar/alveolar adenomas were observed for 1 of 24 (4.2%) female rats at 16 mg/kg/day and 1 of 23 (4.3%) male rats at 2 mg/kg/day. There was no reported spontaneous incidence rate for bronchiolar/alveolar adenoma in 12-13 month studies [redacted]

The mouse micronucleus test and in vivo bone marrow cell chromosomal aberration assay described in the current approved labeling suggests that omeprazole may possess clastogenic activity. For the first assay for chromosomal aberrations in mouse bone marrow conducted by Astra (Study No. 85095), an increased incidence of chromosomal aberrations was observed at the 24 hr sampling interval. However, in the second assay conducted by Merck, methodology deviated significantly from that used in the Astra study as well as published standards in the scientific literature (Mutation Research 189: 157-165, 1987) and the company's own standard operating procedure (see letter from Division to sponsor dated November 30, 1990). The Merck study was deficient with regard to the following parameters: use of weanling animals rather sexually mature animals; use of male animals only rather than animals of both sexes given that gender-related differences in plasma drug levels were known to occur (i.e., plasma drug levels in females were twice those observed in males); and use of less than optimal sampling times (i.e., 6, 24, and 48 hr) given the emphasis on a 12 hr

sampling time in standardized methodology. Results of the second bone marrow chromosomal aberration assay should be considered invalid and disregarded.

A human lymphocyte chromosomal aberration assay submitted to NDA 19,810 as correspondence dated March 29, 2000 demonstrated unequivocally that omeprazole and its R- and S-enantiomers possessed clastogenic activity. See review dated August 9, 2000.

**Recommended Version:**

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the *drug*. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

**2. Pregnancy:**

**Current Labeling:**

Pregnancy Category C

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality,

fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Sponsor's Version:

Evaluation:
#SE8-058 dated October 7, 1998, the sponsor submitted additional reproductive toxicology studies conducted in rats and rabbits with the intention of providing support for a change in the Pregnancy Category Label from C to B. These additional reproductive toxicology studies with omeprazole revealed evidence of adverse effects not observed in earlier studies as well as confirming previously observed toxic effects. In a Segment II teratology study with rats, omeprazole at oral doses ≤320 mg/kg/day produced no structural teratogenic effects; however, toxic effects with regard to behavioral development were evident, which had not been described in earlier studies. A Segment III perinatal and postnatal development study conducted in rats using the oral route of administration confirmed earlier observations of postnatal developmental

toxicity in offspring resulting from maternal treatment with omeprazole. Two additional Segment III studies, conducted by the intravenous route, also confirmed observations of postnatal developmental toxicity in offspring resulting from maternal treatment with omeprazole. It should be noted that the sponsor has not repeated the Segment II teratology study in rabbits using the oral route of administration. These additional studies in the supplement did not change the conclusions of 1989 reviews of reproductive toxicology studies with omeprazole submitted under NDA 19,810. From a preclinical standpoint, it was recommended that omeprazole should remain under Pregnancy Category C.

**Recommended Version:**

Pregnancy Category C

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day and in pregnant rabbits at doses up to 69 mg/kg/day ( body surface area did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**3. Nursing Mothers:**

**Current Labeling:**

It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Sponsor's Version:**

"Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This would correspond to 0.004 mg of omeprazole in 200 ml of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in

nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

Evaluation: From a preclinical standpoint, the sponsor's version appears acceptable.

Evaluation:

Recommended Version:

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## SUMMARY AND EVALUATION:

Omeprazole (Prilosec®) is an inhibitor of gastric parietal cell $H^+,K^+$-ATPase. Omeprazole has been marketed as a prescription drug for short-term treatment of active duodenal ulcer, treatment of gastroesophageal reflux disease (GERD), treatment of heartburn and other symptoms associated with GERD, short-term treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis). In NDA 19,810 Supplement #SE8-058 dated October 7, 1998, the sponsor submitted additional preclinical and clinical studies with the intention of providing support for a change in the Pregnancy Category Label from C to B. In a letter from the Division to the sponsor dated October 7, 1999, this information was determined to be inadequate and the supplemental application was not approvable. Thus, omeprazole remained under Pregnancy Category C. In the present submission, the sponsor has provided proposed changes in approved labeling as well as an integration of laboratory and human pregnancy data on omeprazole (i.e., Wedge Model) with the intention of providing support for a change in Pregnancy Category Label from C to B.

The sponsor provided an integration of laboratory and human pregnancy data on omeprazole using a "Wedge model"; however, preclinical findings in reproductive toxicology studies were not accurately represented. Findings in reproductive toxicology studies with omeprazole are listed below followed by an integration of laboratory and human pregnancy data using the "Wedge model". In a Segment I fertility and reproductive performance study in rats, oral treatment with omeprazole at 13.8, 43.1, and 138 mg/kg/day produced a dose-related increase in post-implantation losses and consequently a decrease in number of live pups. For dams allowed to deliver, dose-related decreases in viability and body weight gains for pups were also observed. In a Segment II teratology study in rats, oral treatment with omeprazole at 3.2, 32, and 320 mg/kg/day produced no structural teratogenic effects; however, toxic effects with regard to behavioral development were evident at the mid and high doses. In a Segment II teratology study in rabbits, oral treatment with omeprazole at 6.9, 27.6, and 69.1 mg/kg/day was disruptive to pregnancy as well as embryotoxic and fetotoxic as it produced dose-related increases in embryonic deaths/dam and in percent fetal loss. Omeprazole also produced a dose-related decrease in number of viable fetuses/dam. In two Segment III perinatal and postnatal development studies in rats, oral treatment with omeprazole at 13.8, 43.1, and 138 mg/kg/day or 3.2, 32, and 320 mg/kg/day retarded pup body weight gain up to day 21 postpartum. In Step 1 of the wedge with regard to signal strength, there was cross-species concordance (i.e., rats and rabbits), multiplicity of effects (i.e., embryo/fetal toxicity in rats and rabbits, and postnatal toxicity in rats), no significant evidence of maternal toxicity, and rare effects (i.e., increases in

the incidence of affected animals). The level of concern for signal strength appears to be +4. In Step 2 of the Wedge with regard to pharmacodynamics, there were dose-response relationships for observed effects, dose-response curves were generally steep, there appeared to be no similarity between pharmacologic and toxicological mechanisms, there were multiplicity of effects as a function of time (i.e., embryo/fetal toxicity and postnatal toxicity), and observed effects may or may not be reversible. The level of concern for pharmacodynamic considerations appears to be +3 or +4. In Step 3 of the Wedge with regard to test species concordance with humans, metabolites and metabolic pathways appeared to be similar for rats and humans. The level of concern for test species concordance appears to be +1. In Step 4 of the Wedge with regard to relative exposure, toxic effects in rats and rabbits were observed at doses ranging from 6 to 56 times the human dose based upon a body surface area basis. No observed effect levels were not established in these studies. The level of concern with regard to relative exposures appears to be +1. In Step 5 of the Wedge with regard to class alerts, there appear to be none and the level of concern appears to be 0. Epidemiological data that evaluated fetal risk from women that were treated with Prilosec® during pregnancy were judged to be inadequate. Integration of laboratory and human pregnancy data on omeprazole using the Wedge model appears to indicate a significant level of concern.

**RECOMMENDATION:** Changes in the text of the labeling are needed as outlined in the review portion.

Timothy W. Robison, Ph.D. — Date: 10-24-2000
Pharmacologist

Comments: Concur

Jasti B. Choudary, B.V.Sc., Ph.D. — Date: 10/26/00
Supervisory Pharmacologist

cc:
Orig NDA 19,810
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

R/D Init.: J. Choudary 9/29/00

# PHARMACOLOGIST'S REVIEW OF NDA 19,810
## (Supplement # SE8 058 Amendments dated September 24, 1999 and October 7, 1999)

**Sponsor & Address:** Astra Merck, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

OCT 26 1999

**Reviewer:** Timothy W. Robison, Ph.D.
Pharmacologist, HFD-180

**Date of Submission:** September 24, 1999
October 7, 1999

**Date of HFD-180 Receipt:** September 27, 1999
October 8, 1999

**Date of Review:** October 26, 1999

**Drug:** Prilosec (Omeprazole) Delayed-Release Capsules.

**Category:** Inhibitor of gastric parietal cell $H^+,K^+$-ATPase inhibitor, Proton pump inhibitor.

**Submission Contents:**

The sponsor has responded to questions from the Division regarding Supplement # SE8 058 submitted on October 7, 1998. For each question, the sponsor's response is summarized within quotations followed by an evaluation of this response.

1. Were the reproductive toxicology studies conducted by / of Japan performed in compliance with United States FDA Good Laboratory Practice Guidelines? If different regulatory guidelines were used for conduct of these studies, how do they differ from United States FDA Good Laboratory Practice Guidelines?

**Sponsor's Response:** "The study reports for all reproductive toxicology studies conducted by / / Japan, with the exception of Report No. R-360, contain statements indicating that the studies were conducted in accordance with either Yakuhatsu [Notification] no. 313, "Standards for the performance of pharmaceutical safety studies", of March 31, 1982 or Yakuhatsu no. 313 and Yakuhatsu no. 870, "Amended regulations regarding pharmaceutical GLP and audits", of October 5, 1988, depending on time during which the studies were conducted. These notifications are Japanese Ministry of Health and Welfare's GLP regulations for pharmaceuticals. They are equivalent to the US FDA's GLP regulations. For Report No. R-360, a statement of GLP compliance was not included due to premature termination of the study resulting from failure of the air conditioning system supplying the room where animals were housed."

Evaluation: The sponsor's response appears to be adequate.

2. For Report No. R-120, the sponsor should account for the pregnancy status of all $F_0$ dams (i.e., pregnant, not pregnant, infertile).

Sponsor's Response: "For pregnant female rats scheduled for cesarean section, there were 24 animals/group. For rats at 0, 3.2, 32, and 320 mg/kg/day, there were apparently 24, 24, 24, and 22 pregnant dams/group, respectively. Two female rats in the 320 mg/kg/day were not pregnant. For pregnant female rats allowed to deliver their offspring, there were 12 animals/group. For rats at 0, 3.2, 32, and 320 mg/kg/day, there were apparently 11, 11, 12, and 12 pregnant dams/group, respectively. One dam in each of the control and 3.2 mg/kg/day groups was not pregnant."

Evaluation: The sponsor's response appears adequate.

3. For Report numbers R-120, R-249, R-361, R-444, and R-143 in which dams were allowed to deliver their offspring, based upon the numbers of implantations, live born fetuses, and stillborn fetuses, there appeared to be missing fetuses. The sponsor should attempt to account for all fetuses in these reports.

Sponsor's Response: "For these study reports, the dams, that were allowed to deliver, were sacrificed on postpartum day 21 or 22 in the Segment II (Report No. R-120 and Report No. R-249) and Segment III (Report No. R-361 and Report No. R-143) studies. During the necropsy examination of each dam, the number of implantation sites was enumerated. On days 21 or 22, it is not possible to discern resorptions, so only implantation sites can be quantified. Thus, the difference between the number of implantations and the sum of live born plus stillborn fetuses does not represent "missing fetuses", but instead represents resorptions and any unobserved cannibalized fetuses."

Evaluation: Tables presented in the Pharmacology Review of supplement # SE8 058 (Document Room Date: August 11, 1999) were updated based upon this information provided by the sponsor (see tables below). In Report No. R-120, an oral Segment II teratology study in rats, and Report No. R-249, an intravenous Segment II teratology study in rats, the numbers of resorptions and unobserved cannibalized fetuses were not treatment-related. In Report R-361, an intravenous Segment III perinatal and postnatal development study in rats, and Report R-143, an oral Segment III perinatal and postnatal development study in rats, the numbers of resorptions and unobserved cannibalized fetuses were increased for omeprazole treatment groups. These findings parallel decreases in the live birth index for each study. Report number R-444 was not mentioned in the sponsor's response.

**Segment II Study: Oral Teratology Study in Rats (Report No. R-120).**

Delivery data for $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 11 | 11 | 12 | 12 |
| # $F_0$ dams that delivered pups | 11 | 11 | 12 | 11 |
| Gestation period, days | 22.0 | 22.0 | 22.1 | 22.4 |
| Implants/dam | 14.3 (157/11) | 13.7 (151/11) | 14.8 (177/12) | 14.7 (162/11[a]) |
| Stillborn $F_1$ pups | 4 (2.6%) | 5 (3.4%) | 1 (0.6%) | 2 (1.2%) |
| Live $F_1$ pups/dam | 13.7 (151/11) | 12.7 (140/11) | 14.2 (170/12) | 14.5 (160/11) |
| **Resorptions/Unobserved Cannibalized Fetuses** | **2** | **6** | **6** | **0** |
| Male to Female Ratio | 0.99 (75/76) | 1.15 (75/65) | 0.93 (82/88) | 0.90 (76/84) |
| Live birth index, % | 96.2% (151/157) | 92.7% (140/151) | 96.0% (170/177) | 98.8% (160/162) |

a. One dam (#4126) at 320 mg/kg/day did not deliver by day 24 of gestation.

**Segment II Study: Intravenous Teratology Study with Omeprazole in Rats (Report No. R-249).**

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 11 | 12 | 12 | 11 |
| #$F_0$ dams that delivered pups[a] | 11 | 12 | 11 | 11 |
| Gestation period, days | 21.9 | 21.8 | 22.0 | 22.0 |
| Implantation sites/dam | 16.3 (179/11) | 15.8 (189/12) | 16.6 (183/11) | 15.0 (165/11) |
| Stillborn $F_1$ pups (%) | 3 (1.9%) | 9 (5.0%) | 3 (1.8%) | 6 (3.9%) |
| **Resorptions/Unobserved Cannibalized Fetuses** | **18** | **10** | **15** | **11** |
| Live $F_1$ pups/dam | 14.4 (158/11) | 14.2 (170/12) | 15.0 (165/11) | 13.5 (148/11) |
| Male to Female Ratio | 0.95 (77/81) | 1.13 (90/80) | 1.14 (88/77) | 0.90 (70/78) |
| Live birth index, % | 88.3 (158/179) | 89.9 (170/189) | 90.2 (165/183) | 89.7 (148/165) |

a. Status of dams that did not deliver was not given.

**Segment III Study: Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Intravenous Route (Report No. R-361).**

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 24 | 24 | 24 |
| # $F_0$ dams that delivered live pups | 24 | 23 | 23 | 24 |
| Gestation period (days) | 22.4 | 22.3 | 22.4 | 22.3 |
| Implantations/dam | 16.5 (396/24) | 16.0 (369/23) | 15.6 (359/23) | 15.8 (378/24) |
| Live $F_1$ pups/dam | 15.7 (376/24) | 14.6 (335/23) | 14.3 (330/23) | 14.0 (335/24) |
| Live Birth Index,% | 94.9% (376/396) | 90.8% (335/369) | 91.9%* (330/359) | 88.6%* (335/378) |
| Stillborn pups (%) | 10 (2.6%) | 13 (3.7%) | 11 (3.2%) | 16 (4.6%) |

| **Resorptions/Unobserved Cannibalized Fetuses** | **10** | **21** | **18** | **27** |
|---|---|---|---|---|
| Male/Female Ratio | 0.97 (185/191) | 1.13 (178/157) | 0.92 (159/172) | 1.09 (175/160) |
| Fetal body weight, g Male/Female | 6.7/6.3 | 6.8/6.4 | 6.9/6.4 | 6.6/6.3 |

$p \leq 0.05$

Segment III Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Oral Route of Administration **(Report No. R-143).**

Delivery data for $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| **Parameter** | **0 mg/kg/day** | **3.2 mg/kg/day** | **32 mg/kg/day** | **320 mg/kg/day** |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 23 | 24 | 24 |
| # $F_0$ dams that delivered live pups | 24 | 23 | 24 | 23 |
| Gestation period (days) | 21.8 | 21.9 | 21.9 | 22.0 |
| Implantations/dam | 15.2 (364/24) | 15.7 (361/23) | 15.6 (374/24) | 15.9 (381/24) |
| Live $F_1$ pups/dam | 14.5 (347/24) | 14.9 (342/23) | 14.3 (344/24) | 14.0 (336/24) |
| Stillborn pups (%) | 7 (2.0%) | 6 (1.7%) | 11 (3.1%) | 24 (6.7%) |
| **Resorptions/Unobserved Cannibalized Fetuses** | **10** | **13** | **19** | **21** |
| Male/Female Ratio | 0.94 (168/179) | 1.06 (176/166) | 0.94 (167/177) | 1.05 (172/164) |
| Live Birth Index | 95.3 | 94.7 | 92.0 | 88.2 |

Segment III Study: Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Intravenous Route **(Report No. R-444).**

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 10 mg/kg/day from day 17 of gestation to day 21 postpartum.

| **Parameter** | **0 mg/kg/day** | **1 mg/kg/day** | **3.2 mg/kg/day** | **10 mg/kg/day** |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 24 | 23 | 24 |
| # $F_0$ dams that delivered live pups | 24 | 24 | 23 | 24 |
| Gestation period (days) | 22.3 | 22.3 | 22.3 | 22.3 |
| Implantations/dam | 15.9 (381/24) | 15.6 (375/24) | 16.2 (372/23) | 16.5 (397/24) |
| Live $F_1$ pups/dam | 14.0 (335/24) | 14.1 (338/24) | 14.2 (326/23) | 14.7 (352/24) |
| Stillborn pups (%) | 15 (4.3%) | 10 (2.9%) | 15 (4.4%) | 9 (2.5%) |
| **Resorptions/Unobserved Cannibalized Fetuses** | **31** | **27** | **31** | **36** |
| Live Birth Index, % | 87.9 (335/381) | 90.1 (338/375) | 87.6 (326/372) | 88.7 (352/397) |
| Male/Female Ratio | 0.93 (161/174) | 0.91 (161/177) | 0.96 (160/166) | 0.89 (166/186) |
| Fetal body weight, g Male/Female | 6.8/6.4 | 6.8/6.4 | 6.7/6.4 | 6.8/6.4 |

4. Line listings for individual dams were not provided in Report numbers R-241, R-142, or R-120.

Sponsor's Response: "The sponsor provided supporting line listings for individual dams for Report numbers R-142 and R-120. The sponsor claims that supporting line listing for individual dams in Report No. R-241 were given in the Appendices contained within the report."

Evaluation: The sponsor's response appears adequate.

## SUMMARY AND EVALUATION

Omeprazole (Prilosec™) is an approved drug product classified as an inhibitor of gastric parietal cell $H^+,K^+$-ATPase. In Supplement #SE8 058 submitted on October 7, 1998, the sponsor submitted additional reproductive toxicology studies conducted in rats and rabbits with the intention of providing support for a change in the Pregnancy Category Label from C to B. In the present amendments, the sponsor has responded to questions from the Pharmacology Review (Document Room Date: August 11, 1999) of this supplement.

These additional reproductive toxicology studies provided in Supplement #SE8 058 were conducted at / Japan. The sponsor confirmed that these studies were conducted in compliance with Japanese Regulations that are equivalent to the US FDA's GLP regulations. It should be noted that the source of drug varied between studies reviewed under NDA 19,810 in 1989 and studies conducted by / . The source of drug for studies reviewed under NDA 19,810 in 1989 was AB Hassle of Sweden, while the sources of drug for studies conducted by were and

In two Segment II teratology studies in rats (Report numbers R-120 and R-249) and three Segment III perinatal and postnatal development studies in rats (Report numbers R-361, R-444, and R-143) in which dams were allowed to deliver their offspring, there appeared to be missing fetuses based upon the numbers of implantations, live born fetuses, and stillborn fetuses. The sponsor stated that during the necropsy examination of each dam, the number of implantation sites was enumerated. On days 21 or 22 postpartum, it is not possible to discern resorptions, so only implantation sites can be quantified. Thus, the difference between the number of implantations and the sum of live born plus stillborn fetuses does not represent missing fetuses, but instead represents resorptions and any unobserved cannibalized fetuses. Based upon this information provided by the sponsor, reanalysis of Report R-361, an intravenous Segment III perinatal and postnatal development study in rats, and Report R-143, an oral Segment III perinatal and postnatal development study in rats, revealed that the numbers of resorptions and unobserved cannibalized fetuses were increased for omeprazole treatment groups. These findings parallel decreases in the live birth index for each study. These studies appear to confirm the findings of embryo/fetal toxicity found in studies reviewed under NDA 19,810 in 1989.

The additional information provided in these amendments does not alter the recommendations of the Pharmacology Review of Supplement #SE8 058 (Document Room Date: August 11, 1999). This information does confirm the findings of embryo/fetal toxicity found in studies reviewed under NDA 19,810 in 1989.

**RECOMMENDATION:** None.

Timothy W. Robison
Timothy W. Robison, Ph.D.

10-26-99
Date

cc:
Orig NDA 19,810
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

10/26/99

R/D Init.: J. Choudary

TWR/hw/10/25/99
C:\MSWORD\PHARM\N\19810910.0TR

# Memorandum

Date: October 7, 1999

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III
Co-Chair, CDER Reproductive Toxicology Committee

To: Florence Houn, M.D.
Director, ODE III

Cc: Lillia Talarico, M.D., Dir., DGHDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGHDP (HFD-180)
Tim Robison, Ph.D., Pharm./Tox., DGHDP (HFD-180)

Subject: NDA 19-810 S-058
Omeprazole label: Pregnancy subsection

I. Material Reviewed

1. Astra Pharmaceuticals cover letter to NDA 19-810 (SE8-058), dated 10/7/98, accompanied by proposed label changes.
2. Pharmacologist's Review of submitted data, dated 8/11/99.
3. Original Pharmacology and Supervisory Addendum for NDA 19-810, dated 1989.

II. Specific Comments and Recommendations

1. Regardless of the Division's or Office's decision as to whether to grant the sponsor's request for a change in the Pregnancy category of omeprazole from "C" (the current categorization) to "B"

2. Findings and conclusions drawn from the reproductive and developmental toxicity studies conducted with omeprazole must be clearly stated, adequately supported and consistent with current practices in reproductive toxicology.

3. Concerns regarding the GLP nature of several of the newly submitted non-clinical reproductive toxicology studies were stated in the P/T review. These concerns may be summarized as issues of: a) comparability of the Japanese Ministry of Health and Welfare and US FDA guidelines on GLP procedures, b) inclusion of group summary data without individual animal data, and c) animals potentially unaccounted for or otherwise lost from studies (Reports R-120, R-249, R-361, R-444, and R-143.

   Recommendations:

   a) Questions regarding the comparability of the GLP guidelines existing in the US and Japan during the late 1980's and early 1990's, should be referred to DSI for evaluation and comment.
   b) DSI should be asked to determine if the [redacted] was inspected for GLP compliance by US or Japanese regulatory personnel (i.e., under an agreement of mutual recognition) at a time approximating or concurrent with the conduct of the newly submitted studies.
   c) The sponsor should be asked to supply statements regarding the GLP "compliance" or "non-compliance" of each of the newly submitted studies. (This request should be communicated to the sponsor as early in the review process as possible, i.e., on or about the time of the 45 day Filing Meeting for the NDA supplement).
   d) The sponsor and/or the study test site should be asked to account for the apparent discrepancies in animal numbers in studies R-120, R-249, R-361, R-444, and R-143, and to provide individual animal data for each study.)

4. Inspection of the summary dataset suggests that the administration of omeprazole was associated with an increased incidence of pre- and post-implantation losses in rats and rabbits, and evidence of embryofetal/neo-natal toxicity (as evidenced by reduced fetal weight gain and viability) following late gestational exposure. While the original NDA review does not clearly identify those endpoints for which statistically significant effects (above the historical background range) were observed, the dose related trend for multiple effects are clearly evident. Furthermore, these adverse reproductive effects are evident in multiple studies at doses of omeprazole, which demonstrate minimal or no apparent maternal toxicity. Under these circumstances (i.e., embryolethality and reduced growth/viability at maternally non-toxic doses), the observed adverse reproductive effects must be attributed to the investigational drug, as significant maternal toxicity was not evident to account for the adverse reproductive effects.

III. General Comments

1. The preclinical data do not appear to be suggestive of a significant risk of congenital malformations for patients taking omeprazole. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.

2. An increased incidence of embryolethality (evident as pre- and/or post-implantation resorptions and decreased fetal/neonatal viability) was seen in multiple studies and test

species. Since pre-implantation and early post-implantation losses may occur prior to the recognition of human pregnancy, these endpoints are extremely difficult to study in typical clinical settings. Thus, the risk for adverse effects in humans may be inestimable except on the basis of animal data, which is suggestive of a moderate level of risk. A discussion of this potential reproductive risk should be included in the product label.

3. Concerns regarding potential transplacental carcinogenic effects of omeprazole have not been addressed by the sponsor. Since this compound was carcinogenic when tested in a 2-year in-vivo rodent bioassay, and has demonstrated proliferative alterations of the GI mucosa following shorter duration exposure in animals and humans, some level of concern for potential transplacental effects in humans appears reasonable. Since a limited subset of the documents pertaining to omeprazole was included in this review, it is not apparent whether this issue has previously been discussed with the product sponsor.

NDA 19,810

WALSH

# PHARMACOLOGIST'S REVIEW OF NDA 19,810
## (Supplement # SE8 058 Dated October 7, 1998)

**Sponsor & Address:** Astra Merck, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

AUG 11 1999

**Reviewer:** Timothy W. Robison, Ph.D.
Pharmacologist, HFD-180

**Date of Submission:** October 7, 1998

**Date of HFD-180 Receipt:** October 7, 1998

**Date of Review:** August 11, 1999

**Drug:** Prilosec (Omeprazole) Delayed-Release Capsules.

**Category:** Inhibitor of gastric parietal cell $H^+,K^+$-ATPase inhibitor, Proton pump inhibitor.

**Submission Contents:**

| Study Title | Report Number | Report Date | Testing Laboratory | Drug Batch/Source | Page # |
|---|---|---|---|---|---|
| **ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION:** | | | | | |
| **Distribution** | | | | | |
| **Mouse** | | | | | |
| Distribution of $^{14}$C-Omeprazole in Mice After Intravenous or Oral Administration. | T 1177 | | | | 3 |
| Placental Transfer of Omeprazole in Maternal and Fetal Sheep (Developmental Pharmacology and Therapeutics 9: 323-331, 1986). | | | | | 3-4 |
| **Metabolism and Excretion** | | | | | |
| **Rat** | | | | | |
| Distribution, Metabolism, and Excretion in Rats After Intravenous Administration of Omeprazole. | | | | | 4-6 |
| **TOXICOLOGY:** | | | | | |
| **Reproductive Toxicology** | | | | | |
| **Rat** | | | | | |
| Segment I Fertility and Reproductive Performance Study in Rats Using Oral Administration. | T 1343 | 12/8/82 | AB Astra Toxicology Laboratories Sweden | Batch No. H24:1/AB Hassle | A |
| Segment I Fertility and Reproductive Performance Study in Rats Using I.V. Administration. | R-241 | 2/13/90 | | | 7-11 |

| | | | | | |
|---|---|---|---|---|---|
| Segment I Fertility and Reproductive Performance Study in Rats Using Oral Administration. | R-142 | 1/20/88 | | | 12-15 |
| Segment II Teratology Study in Rats Using Oral Administration. | T 1328 | 1/18/82 | AB Astra Toxicology Laboratories Sweden | Batch number 124/80 /AB Hassle | A |
| Segment II Teratology Study in Rats Using Intravenous Administration. | R-249 | 3/9/90 | | | 15-21 |
| Segment II Teratology Study in Rats Using Oral Administration. | R-120 | 9/25/87 | | | 21-28 |
| **Rabbit** | | | | | |
| Segment II Teratology Study in Rabbits Using Oral Administration. | T 1316 | 12/21/81 | AB Astra Toxicology Laboratories Sweden | Batch number 124/80 /AB Hassle | A |
| Segment II Teratology Study in Rabbits Using Intravenous Administration. | R-399 | 3/31/92 | | | 28-32 |
| **Rat** | | | | | |
| Segment III Perinatal and Postnatal Development Study in Rats Using Oral Administration. | T 1485 | 10/21/83 | AB Astra Toxicology Laboratories Sweden | Batch numbers HT 134-1-14, HT 136-1-8, HT 140-1-4, and HT 141-1-6 /AB Hassle | A |
| Segment III Study: Extended Perinatal and Postnatal Study in Rats After Oral Administration of Omeprazole During Late Pregnancy and Lactation. | T 1747 | 3/4/86 | AB Astra Toxicology Laboratories Sweden | Batch numbers HT 134-1-20 and HT 141-1-10 /AB Hassle | A |
| Segment III Perinatal and Postnatal Development Study in Rats Using Intravenous Administration. | R-361 | 2/20/92 | | | 2-37 |
| Segment III Perinatal and Postnatal Development Study in Rats Using Intravenous Administration. | R-444 | 11/19/92 | | | 7-39 |
| Segment III Perinatal and Postnatal Development Study in Rats Using Oral Administration. | R-143 | 1/20/88 | | | 40-44 |

A. These studies were part of NDA 19,810 submitted on June 30, 1988; although, they have been resubmitted as part of the present supplement. Current approved Pregnancy labeling is based upon these studies in agreement between the FDA and the sponsor (Merck). For reviews of these studies, see the Pharmacologist's Review of NDA 19,810 (Document Room Date: May 25, 1989) and the Supervisory Pharmacologist's Addendum (Document Room Date: May 30, 1989).

## ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION:

### Distribution

### Mouse

**Whole-Body Autoradiographic Study on the Distribution of $^{14}$C-Omeprazole ($^{14}$C-168/68) in Mice After a Single Intravenous or Oral Administration (Report No. T 1177).**

Methods: The tissue distribution of $^{14}$C-omeprazole was examined in mice using the Ullberg whole-body autoradiographic method. Pregnant female mice received omeprazole by the intravenous route at a dose of 3.12 mg/kg. Mice were sacrificed at 5 and 15 min and 1, 4, and 16 hr after dosing. Due to the apparent late stage of pregnancy, the mice, designated for sacrifice at 16 hr after dosing, delivered the litter before sacrifice. The newborn mice were treated in the same manner as the mother. The tissue distribution was also examined in male mice that received radiolabeled omeprazole at a dose of 5.2 mg/kg by either the oral or intravenous route.

Results: Following intravenous administration of radiolabeled omeprazole to pregnant mice, significant levels of radioactivity were associated with the ovaries and amniotic sack at 15 min after dosing; although, radioactivity was evident in the placenta and fetal liver and intestinal contents. At 1 hr after dosing, high levels of radioactivity were evident in the amniotic sack and fetal urinary bladder and intestinal contents. Following oral or intravenous administration of radiolabeled omeprazole to male mice, high levels of radioactivity were evident in the gastric mucosa, parts of the stomach, gall bladder or bile ducts, parts of the intestinal contents, and urinary bladder within 1 to 5 min after dosing and continuing up to 4 hr after dosing. Radioactivity in the gastric mucosa continued to persist at time points after 4 hr.

### Sheep

**Placental Transfer of Omeprazole in Maternal and Fetal Sheep (Developmental Pharmacology and Therapeutics 9: 323-331, 1986).**

Methods: Studies were performed in pregnant Merino or Dorset-Horn sheep during the last 2 weeks of gestation (term = 147 days). The low dose group received an initial intravenous bolus dose of omeprazole at 0.15 mg/kg followed a 3 hr intravenous infusion at 0.21 mg/hr/kg. The high dose group received an initial intravenous bolus dose at 0.61 mg/kg followed a 3 hr intravenous infusion at 0.84 mg/kg/hr. Maternal blood was collected at time points ranging from 5 to 180 min after the bolus dose. Fetal blood in the low dose group was collected at time points ranging from 5 to 180 min after the bolus dose, but in the high dose group, it was collected at time points from 75 to 165 min. Maternal and fetal urine were collected serially at time points ranging from 60 to 180 min. Protein binding of omeprazole was measured in the high dose group using an ultrafiltration method. Omeprazole concentrations were measured by HPLC.

Results: For the low dose group, the mean total steady-state omeprazole concentrations in the mother and fetus were 556 and 101 ng/mL, respectively. For the high dose group, the mean total omeprazole concentrations in the mother and fetus were 2660 and 563 ng/mL, respectively. The transplacental gradient was approximately 5 to 1 in both the low and high dose groups. The unbound drug fraction in mother and fetus were 6.6 and 11.9%, respectively, which accounted, in part, for the 5 to 1 maternal to fetal gradient of total drug concentration. Total systemic clearance in adult sheep was 349 ± 179 mL/min. Urinary clearance of omeprazole was low in both mother (0.137 mL/min) and fetus (0.067 mL/min) suggesting extensive hepatic clearance of drug in the mother. The principal determinant of fetal exposure was the systemic clearance of unbound drug in the mother.

## Metabolism and Excretion

### Rat

### Distribution, Metabolism, And Excretion in Rats After Single Intravenous Administration of Omeprazole Sodium.

Methods: Distribution of the radiolabeled omeprazole into fetuses and lactating pups were examined with pregnant and lactating rats, respectively. Further, radiolabeled drug was administered by the intravenous route to male and female Sprague-Dawley rats to examine its distribution, metabolism, and excretion. Omeprazole was labeled with $^{14}C$ in the second position of the benzimidazole ring. For determination of plasma metabolites, radiolabeled omeprazole was administered at an intravenous dose of 25 mg/kg. For other studies, radiolabeled omeprazole was administered at an intravenous dose of 5 mg/kg. Radioactivity levels in blood, plasma, tissues, milk, urine, and feces were measured with a liquid scintillation counter. Omeprazole and metabolites in plasma, urine, and feces were separated by HPLC with UV detection. Following HPLC, omeprazole and metabolites were separated by two-dimensional TLC, autoradiograms of TLC plates were made, and spots relative to known standards were collected and the quantity of radioactivity was determined.

Results:

1. Fetal Levels of Radioactivity: $^{14}C$-omeprazole was administered by the intravenous route to pregnant female rats on day 18 of gestation. Animals were sacrificed at time points between 5 min and 24 hr after dosing and specified tissues (i.e., maternal plasma, blood, whole brain, heart, lungs, liver, kidneys, adrenals, uterus, ovaries, and mammary glands, placenta, amniotic fluid, fetus (whole body), and fetal blood, brain, heart, liver, and kidneys) were collected for determination of radioactivity content. Peak concentrations of radioactivity in the placenta, amniotic fluid, and fetus (whole body) occurred at 5 min after dosing. Concentrations of radioactivity in the placenta and amniotic fluid were 38.1 and 12.7% of the maternal plasma concentration (9.303 $\mu$g equiv./mL), respectively. For the fetus (whole body) at 5 min after dosing, the concentration of radioactivity was 43.2% of the plasma concentration and the fetal

content of radioactivity was 0.43% of the administered dose. Fetal blood content of radioactivity at 5 min after dosing was 60.3% of the maternal plasma concentration. Radioactivity in fetal tissues (i.e., brain, heart, lung, liver, and kidney) at 5 min after dosing ranged from 18.3 to 34% of the maternal plasma concentration.

2. Radioactivity Concentrations in Milk: $^{14}$C-omeprazole was administered by the intravenous route to dams on the 9$^{th}$ day postpartum. Milk and blood samples were collected at time points between 5 min and 48 hr after dosing. Oxytocin was administered to dams immediately prior to collection of milk samples. At 5 min after dosing, milk content of radioactivity was 66% of the plasma concentration. However, from 2 to 48 hr after dosing, milk content of radioactivity was 3.1-7.8 times the plasma concentration. Two-dimensional TLC analysis found that 50% of the radioactivity in milk at 5 min after dosing was the parent compound; however, by 6 hr after dosing, levels of the parent compound were undetectable.

3. Measurement of Radioactivity Concentrations in Blood and Plasma of Male and Female Rats: Radiolabeled omeprazole was administered by the intravenous route to male and female rats at a dose of 5 mg/kg. Blood was collected at time points ranging from 5 min to 168 hr after dosing. The terminal half life of radioactivity in blood (4.4 to 7.3 days) was significantly longer as compared with plasma (9.1-10 hr), possibly due to covalent association of a radiolabeled metabolite with red blood cells.

4. Plasma Omeprazole and Metabolite Concentrations: $^{14}$C-omeprazole was administered by the intravenous route to male and female rats at 25 mg/kg. Blood samples were collected at time points from 5 min to 12 hr after dosing. Plasma AUC values for omeprazole in male and female rats were 34.7 and 45.1% of the AUC values for total radioactivity, respectively. Volume of distribution values (0.487-5.489 L/kg) significantly exceeded the blood volume (0.054 L/kg) suggesting extensive distribution of omeprazole-related radioactivity into the tissues. Clearance values for omeprazole (1.834-2.857 L/hr/kg) were greater than or equal to hepatic (1.91 L/kg/hr) and renal (1.28 L/kg/hr) plasma flows (Pharmaceutical Research 10: 1093-1095, 1993), suggestive of a rapid metabolic clearance. Clearance values for total radioactivity (0.828-0.992 L/hr/kg) were less than hepatic or renal plasma flows.

5. Whole-Body Autoradiography: The distribution of $^{14}$C-omeprazole in rats following intravenous administration was determined by autoradiography at time points ranging from 5 min to 72 hr after dosing. At 5 min after dosing, radioactivity was widely distributed. At 2 and 6 hr after dosing, high level of radioactivity were observed in the intestinal contents, urine in the bladder, stomach, milk, thyroid gland, kidneys, stomach contents, and liver. At 24 hr after dosing, significant levels of radioactivity were still observed in the intestinal contents, stomach, stomach contents, urine in the bladder, blood, thyroid gland, kidneys, liver, lung, and spleen. At 72 hr after dosing, radioactivity was still observed in the thyroid gland, blood, lungs, liver, kidneys, and gonads.

6. Measurement of Tissue Radioactivity Concentrations: $^{14}$C-omeprazole was administered by the intravenous route to male rats, and tissue contents of radioactivity were determined at time points ranging up to 72 hr after dosing. Peak tissue levels of radioactivity were generally observed at 5 min after dosing. At 5 min, the highest levels of radioactivity were observed in the liver and kidneys, which were 3.2 and 1.9 times the plasma concentration (6.592 $\mu$g equiv./mL). At 2 hr after dosing, the highest tissue concentrations of radioactivity were found in the glandular stomach and thyroid gland, which were 13 and 8.8 times the plasma concentration (0.173 $\mu$g equiv./mL). At 6 hr after dosing, the highest concentration of radioactivity was observed in the large intestines, while contents of other tissues were similar to values at 2 hr. At 24 and 72 hr after dosing, tissue contents of radioactivity had declined to <10% of peak values.

7. Excretion of Radioactivity and Metabolites in the Urine and Feces: $^{14}$C-omeprazole was administered by the intravenous route to male and female rats. Urine and feces were collected at specified intervals until 168 hr after dosing. Fecal excretion was primary route for elimination of radioactivity as it accounted for 54.7 to 61.4% of the administered dose. Omeprazole and 8 metabolites were detected in the urine. Four metabolites were detected in feces, but the parent drug was not found. Omeprazole was metabolized by oxidation and reduction of the sulfinyl group, hydroxylation of the benzimidazole ring, hydroxylation of the side-chain methyl group, O-demethylation, elimination of the benzimidazole ring, and sulfate conjugation of the hydroxyl groups produced by these reactions.

8. Measurement of Biliary Excretion of Radioactivity: Biliary excretion of radioactivity was determined in bile duct-cannulated male rats that received $^{14}$C-omeprazole. Bile, urine and fecal samples were collected at specified intervals until 48 hr after dosing. Biliary excretion was the major route for elimination of omeprazole-related radioactivity as it accounted for 54.4% of the administered dose. More than 40 radioactive metabolites were detected in bile.

9. Measurement of Enterohepatic Circulation of Radioactivity: $^{14}$C-omeprazole was administered by the intravenous route to bile duct-cannulated male rats and bile was collected for a period of 24 hr after dosing. The collected bile was administered by the intraduodenal route to a second set of bile duct-cannulated male rats and bile, urine, and feces were collected at specified intervals until 48 hr after dosing. Following intraduodenal administration of bile containing omeprazole-related radioactivity, the majority of radioactivity was eliminated in the feces .

**TOXICOLOGY:**

Reproductive Toxicology

Rat

Segment I Study: Effects of Intravenous Administration of Omeprazole on Fertility and General Reproductive Performance in Rats (Report No. R-241).

Testing Laboratory:

Date Started: April 3, 1989 (Receipt of animals)

Date Completed: February 13, 1990 (Translated from Japanese to English: June 15, 1998)

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies," Yakuhatsu no. 870 (Pharmaceutical Affairs Bureau directive dated October 5, 1988), entitled "Amended regulations regarding pharmaceutical GLP and audits," and Yakushin no. 1.24 (directive of the Pharmaceutical Affairs Bureau Audit chief and Biological Preparations Department dated September 11, 1988), entitled "Guidelines for the toxicity studies required for requesting approval to manufacture (import) a pharmaceutical." A statement of compliance with the Quality Assurance Unit was included.

Animals: [illegible] were used in this study. Male rats at the start of treatment were 6 weeks old and had a body weight range of 182-219 g. Female rats at the start of treatment were 13 weeks old and had a body weight range of 232-338 g.

Drug Batch: Omeprazole sodium, Lot No. 14 [illegible]

Methods: In a Segment I study, the effects of omeprazole administered by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day were assessed on fertility and reproductive performance in male and female Sprague-Dawley rats. Control animals received the vehicle, [illegible] The pH values of the solution at doses of 0, 10, 32, and 100 mg/kg/day prior to start of treatment with male rats were 10.80, 9.87, 10.30, and 10.80, respectively. The pH of the solution at doses of 0, 10, 32, and 100 mg/kg/day prior to the end of treatment with pregnant female rats were 11.25, 10.54, 10.81, and 11.25, respectively. Male rats were treated for 9 weeks prior to mating, during the mating period, and up to the day before sacrifice. Female rats were treated for 2 weeks prior to mating, during the mating period, and to day 7 of gestation. The sponsor's dose selection was based upon a 2-week intravenous dose range finding

study with rats that received doses of 10, 30, and 100 mg/kg/day. At the high dose of 100 mg/kg/day, transient decreases in spontaneous movements, tachypnea, and clonic convulsions were observed immediately after dosing in both male and female rats. Weight gain was reported to be slightly suppressed in male rats that received 100 mg/kg/day; although, no quantitation was provided. In the present study, there were 22 rats/sex/group. Vehicle or drug solution was administered into the caudal veins using a dose volume was 3 mL/kg. During the treatment period, animals were monitored for clinical signs of toxicity three times per day, prior to dosing, immediately after dosing, and 1 hr after dosing. At other times, animals were monitored twice daily. Male and female rats were weighed twice per week during the pre-mating administration period and the mating period. Female rats were weighed on days 0-7, 11, 14, 17, and 20 of gestation. Data from the mating period was excluded from statistical analysis. Food consumption was measured on the same days that animals were weighed during the pre-mating administration period and on days 1, 4, 7, 11, 14, 17, and 20 of gestation. Estrous cycle was monitored during the pre-mating administration period and the mating period. Female rats confirmed to have a vaginal plug or sperm in the vaginal smear were taken as female rats confirmed to have mated and that day was designated as day 0 of pregnancy. Most of the male rats confirmed to have mated were sacrificed and subjected to a gross autopsy. The testes and epididymides were removed, weighed, and fixed. The prostate, seminal vesicles, and any abnormal sites were also removed and fixed. Histopathological analysis of the testes, epididymides, prostate, and seminal vesicles were performed for male rats whose female partners were infertile despite confirmed mating. For female rats that did mate, the ovaries and uterus were removed, weighed, fixed, and subjected to histopathological analysis. For female rats with confirmed mating, animals were sacrificed on day 20 of pregnancy and subjected to a gross autopsy. The ovaries and uterus were removed and examined to confirm pregnancy. For pregnant female rats, the number of corpora lutea, number of implantations, number of viable fetuses, and number of dead and resorbed fetuses were determined. The placentas for viable fetuses were weighed. The ovaries and uterus of infertile female rats at the time of C-section were removed, weighed, fixed, and subjected to histopathological examination. Viable fetuses were examined for external malformations and variations, their sex was determined, and weighed. Approximately one-half of the viable fetuses of each dam were examined for visceral malformations and variations. Remaining fetuses were examined for skeletal malformations and variations. With regard to external, visceral, or skeletal examinations of $F_1$ fetuses, it should be noted that drug was not administered during the period of organogenesis.

**Results:**

**1. Observed Effects:** Clinical signs of toxicity were observed in male rats at 32 and 100 mg/kg/day and female rats at 100 mg/kg/day.

Clinical signs of toxicity for male treatment groups were recorded from days 0 to 63. For all male rats at 100 mg/kg/day, transient decreases in spontaneous movements, tachypnea, and clonic convulsions were observed immediately after dosing from days 0 to 63. Transient salivation was observed for 7 male rats at 100 mg/kg/day beginning during week 5 and was observed in all male rats at 100 mg/kg/day after week 7. Eight male rats at 100 mg/kg/day were observed in a prone position during week 8. Head

shaking was observed for a total of 4 male rats at 32 mg/kg/day beginning during week 6 and continued through week 9. Swelling or purple discoloration of the tail, attributed to local irritation produced by the test substance, was observed in the 100 mg/kg/day group beginning after 4 weeks of treatment and a total of 12 animals in this group were found with this condition. For 4 of these 12 male rats at 100 mg/kg/day, necrosis and desquamation around injection sites made it impossible to continue to drug administration (4005: after day 39; 4006: after day 41; 4010, after day 42, and 4018: after day 49).

Clinical signs of toxicity for female rats were recorded during pre-mating and gestation periods. For all female rats at 100 mg/kg/day, transient decreased spontaneous movements, tachypnea, and clonic convulsions were observed immediately after dosing throughout the pre-mating period and days 0-7 of gestation. Decreases in spontaneous movement were most prevalent on days 1 and 2 of treatment in female rats at 100 mg/kg/day and all animals were observed in a prone position. Transient salivation was observed immediately after dosing in a sporadic manner beginning on day 2 of treatment and a total of 14 animals during the pre-mating period and 7 animals during days 0 to 7 of gestation were affected.

2. Mortality: One male at 100 mg/kg/day (#4018) was observed with necrosis and desquamation around the injection site after 4 weeks of treatment. Treatment was discontinued to this animal on day 49 due to the inability to administer drug, because of injury around injection sites. This animal developed a massive hemorrhage at the site of desquamation and died on day 63.

3. Body weight and Food consumption: There were no treatment-related effects on body weight gain or food consumption for $F_0$ male rats during the pre-mating period from days 0 to 63 or $F_0$ female rats during the pre-mating period from day 0 to 14 or during the gestation period from days 0 to 7.

4. Fertility and Reproductive Performance: Two dams each at doses of 10, 32, and 100 mg/kg/day were infertile despite confirmed copulation; however, there was no evidence of a dose response relationship. Omeprazole administered by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day to male and female Sprague-Dawley rats had no significant effects on fertility or reproductive performance. Implantation sites/dam at 100 mg/kg/day were decreased to 12.4 as compared to 14.7 for the control. Pre-implantation loss at 100 mg/kg/day was increased to 21.6% as compared to 10.2% for the control. Live fetuses/dam at 100 mg/kg/day were decreased to 11.2 as compared to 13.7 for the control. Live male fetuses/dam at 100 mg/kg/day were decreased to 5.7 as compared to 7.3 for the control; although, there was no significant change in the male to female ratio.

Copulation and insemination indexes for male rats that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day ($1^{st} + 2^{nd}$ matings).

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| N | 22 | 22 | 22 | 18[a] |
| Male copulation index, % | 100 (22/22) | 100 (22/22) | 100 (22/22) | 100 (18/18) |
| Male insemination index, % | 100 (22/22) | 90.9 (20/22) | 90.9 (20/22) | 88.9 (16/18) |

a. Treatment was discontinued in 4 males at 100 mg/kg/day due to necrosis and desquamation at injection sites on the tail.

Copulation and fertility indexes for female rats that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day ($1^{st} + 2^{nd}$ matings).

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| N | 22 | 22 | 22 | 22 |
| Female copulation index, % | 100 (22/22) | 95.5 (21/22) | 100 (22/22) | 100 (22/22) |
| Female fertility index, % | 100 (22/22) | 90.6 (19/21) | 90.9 (20/22) | 90.9 (20/22) |

Reproductive parameters for female rats that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| Number of pregnant dams | 22 | 19 | 20 | 20 |
| Corpora lutea/dam | 16.4 (361/22) | 15.2 (289/19) | 16.2 (323/20) | 15.8 (315/20) |
| Implantations/dam | 14.7 (324/22) | 13.3 (252/19) | 13.8 (276/20) | 12.4 (247/20) |
| Pre-implantation loss, % | 10.2% (37/361) | 12.8% (37/289) | 14.6% (47/323) | 21.6% (68/315) |
| Resorptions, %<br>-Total<br>-Early<br>-Late | <br>7.1 (23/324)<br>7.1 (23/324)<br>0 | <br>13.9 (35/252)<br>13.1 (33/252)<br>0.8 (2/252) | <br>6.9 (19/276)<br>6.2 (17/276)<br>0.7 (2/276) | <br>9.7 (24/247)<br>9.7 (24/247)<br>0 |
| Live fetuses/dam | 13.7 (301/22) | 11.4 (217/19) | 12.9 (257/20) | 11.2 (223/20)* |
| Male fetuses/dam | 7.3 (161/22) | 5.7 (108/19) | 6.4 (127/20) | 5.7 (113/20)* |
| Female fetuses/dam | 6.4 (140/22) | 5.7 (109/19) | 6.5 (130/20) | 5.5 (110/20) |
| Male: Female Ratio | 1.15 | 0.99 | 0.98 | 1.03 |
| Fetal body weight, g<br>Male/Female | <br>3.60/3.41 | <br>3.76/3.45 | <br>3.64/3.41 | <br>3.65/3.40 |
| Placental weight, g | 0.52 | 0.55 | 0.53 | 0.59* |

* $p \leq 0.05$.

5. **Examination of $F_0$ Male and Female Rats:** Right and left epididymis weights for male rats at 100 mg/kg/day were decreased to 94.1 and 95.1% of control values (594.0 and 584.6 mg); although, there were no corresponding histopathological findings. There were no significant histopathological findings in animals that did mate or were infertile.

6. **Fetal Examinations:** There were no treatment-related external, visceral, or skeletal malformations or variations in $F_1$ fetuses; however, it should be noted that drug was not administered during the period of organogenesis. The incidence of the skeletal variation, cervical rib, was increased at doses of 32 and 100 mg/kg/day. The incidence of the skeletal variation, wavy ribs, was increased for all omeprazole treatment groups. Number of ossified metatarsus, both left and right, were decreased at 10 and 100 mg/kg/day; however, no dose response relationship was present.

Visceral examination of $F_1$ fetuses from $F_0$ rats that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| Number of fetuses examined | 144 | 105 | 124 | 108 |
| Dilatation of renal pelvis | 0 | 2 (1.9%) | 2 (1.6%) | 0 |
| Dilatation of ureter | 0 | 2 (1.9%) | 2 (1.6%) | 0 |
| Left umbilical artery | 1 (0.7%) | 1 (1.0%) | 2 (1.6%) | 1 (0.9%) |

Skeletal examination of $F_1$ fetuses from $F_0$ rats that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| Number of fetuses examined | 157 | 112 | 133 | 115 |
| Cervical rib (V) | 2 (1.3%) | 1 (0.9%) | 4 (3.0%) | 4 (3.5%) |
| Wavy ribs (V) | 0 | 1 (0.9%) | 1 (0.8%) | 2 (1.7%) |
| Progress of ossification<br>Number of ossified sternebrae, %<br>6th | 93% (146/157) | 93.8%(105/112) | 99.2%(132/133) | 100%(115/115) |
| Number of ossified metatarsus<br>-right<br>-left | <br>4.95<br>4.95 | <br>4.72*<br>4.72* | <br>4.85<br>4.84 | <br>4.74*<br>4.74* |

In a Segment I study, the effects of omeprazole administered by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day were assessed on fertility and reproductive performance in male and female Sprague-Dawley rats. Male rats were treated for 9 weeks prior to mating, during the mating period, and up to the day before sacrifice. Female rats were treated for 2 weeks prior to mating, during the mating period, and to day 7 of gestation. Omeprazole at intravenous doses ≤ 100 mg/kg/day had no effect on fertility and reproductive performance in rats. Clinical signs of toxicity for $F_0$ male and female rats at 100 mg/kg/day consisted of transient decreases in spontaneous movements, tachypnea, and clonic convulsions immediately after dosing. The observations of clonic convulsions and tachypnea at 100 mg/kg/day suggest that the high dose may have been excessively toxic; although, there were no effects on fertility or reproductive performance. One $F_0$ male rat at 100 mg/kg/day died due to hemorrhage associated with localized irritation produced by test compound at the injection site. Implantation sites/dam at 100 mg/kg/day were decreased to 12.4 as compared to 14.7 for the control. Pre-implantation loss at 100 mg/kg/day was increased to 21.6% as compared to 10.2% for the control. Live fetuses/dam at 100 mg/kg/day were decreased to 11.2 as compared to 13.7 for the control. No listings were provided for individual animals.

Segment I Fertility and Reproductive Performance Study in Rats Treated Orally with Omeprazole (Report #R-142).

Testing Laboratory:

Date Started: March 16, 1987

Dated Completed: January 20, 1988
(Translated from Japanese to English, June 12, 1998)

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies." A statement of compliance with the Quality Assurance Unit was included.

Animals: line rats were used in this study. At the start of treatment, male rats were 6 weeks old and female rats were 13 weeks old. Body weight ranges were 176-197 g for male rats and 222-302 g for female rats.

Drug Batch: Omeprazole, Lot No. 124

Methods: In a Segment I study, the effect of omeprazole on fertility and reproductive performance were assessed in male and female Sprague-Dawley rats. Omeprazole was administered by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day. The sponsor's dose selection was based upon a previous Segment I study (Study #T1343) in which the high dose of 138 mg/kg/day had only slight effects on embryos and fetuses as well as a Segment II study in which the high dose of 320 mg/kg/day affected body weight and food consumption. There were 24 rats/sex/group. Omeprazole

The dose volume was 5 mL/kg. Male rats were treated with vehicle or omeprazole for 9 weeks prior to mating, during the mating period, and until the day prior to sacrifice. Female rats were treated with vehicle or omeprazole for 2 weeks prior to mating, during the mating period, and until day 7 of gestation. During the treatment period, animals were monitored for clinical signs of toxicity three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. At other times, animals were monitored twice per day. Animals were weighed twice per week during the pre-mating and mating periods, and on days 0-7, 9, 11, 14, 17, and 20 of gestation. Food consumption was measured twice per week during the pre-mating and mating periods, and on days 1, 4, 7, 11, 14, 17, and 20 of gestation. The estrus cycle was monitored in female rats during the 2-week pre-mating period. During the mating period, male and female rats were housed together overnight in a ratio of 1 to 1 within the same dose group. Female rats found to have vaginal plugs or confirmed to have sperm in the vaginal smear the next morning were assumed to have mated and this day was taken as day 0 of gestation. After the mating

period, male rats were sacrificed, subjected to a gross pathological examination, and the testes and epididymides were removed, weighed, and fixed. The prostate, seminal vesicles, and abnormal sites were also removed and fixed. Histopathological examination of the testes, epididymides, prostates, and seminal vesicles were performed. Female rats, that were confirmed to have mated, were sacrificed on day 20 of gestation. The ovaries and uteri were removed, weighed, and the number of corpora lutea, number of implantations, number of viable fetuses, and number of dead and resorbed fetuses were determined in pregnant female rats. For infertile female rats, the ovaries and uteri were removed, weighed, fixed, and subjected to histopathological examination. Animals that were not confirmed to have mated, but confirmed to be pregnant were included in the calculation of the mating and fertility indexes, but data collected during gestation, cesarean section data, and organ weight data were excluded from statistical treatment. Viable fetuses were examined for external anomalies, sex was determined, and body weight was measured. Approximately one-half of the fetuses were examined for visceral anomalies of the head, chest, and abdomen and remaining fetuses were examined for skeletal anomalies, skeletal variations, and ossification progress. It should be noted that drug was not administered during the period of organogenesis.

**Results:**

1. **Observed Effects:** Salivation was observed immediately after dosing for male and female rats that received omeprazole at 320 mg/kg/day. For male rats, salivation appeared in 2 animals on day 9 and was observed in a total of 19 animals over the 63 days of treatment. For female rats, salivation appeared in 2 animals on day 6 of the pre-mating period and was observed in a total of 13 animals by the end of treatment (day 7 of pregnancy).

2. **Mortality:** None.

3. **Body Weight and Food Consumption:** Body weight gain was reduced for male rats at 320 mg/kg/day. Body weight gains were reduced for female rats at 320 mg/kg/day during the pre-mating period and for female rats at 32 and 320 mg/kg/day from days 0 to 7 of gestation. Body weights for male controls on days 0 and 63 were 186.5 and 495.6 g, respectively. Body weight gains for male rats at 3.2, 32, and 320 mg/kg/day from days 0 to 63 were 99.8, 97.3, and 85.8% of the control, respectively. Food consumption for male treatment groups was unaffected. Body weights for female controls on days 0 and 14 of the pre-mating period were 255.8 and 267.1 g, respectively. Body weight gains for female rats at 3.2, 32, and 320 mg/kg/day during the pre-mating period were 111.7, 114.9, and 35.2% of the control, respectively. Food consumption for female rats at 320 mg/kg/day was reduced to 85.7% of the control (19.4 g/rat/day). Body weights for female controls on days 0 and 7 of gestation were 269 and 292.9 g, respectively. Body weight gains for female rats at 3.2, 32, and 320 mg/kg/day from days 0 to 7 of gestation were 95.7, 82.5, and 67.8% of the control, respectively. Food consumption was unaffected for female treatment groups during the period of gestation.

4. Fertility and Reproductive Performance: Days until mating and indexes of mating and fertility were unaffected by omeprazole treatment at doses ≤320 mg/kg/day. Reproductive parameters (i.e., corpora lutea/dam, implantation sites/dam, pre-implantation loss, resorbed or dead fetuses, live fetuses/dam, male to female ratio, and fetal body weight) were unaffected by omeprazole treatment.

Mating and fertility indexes for male and female rats that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Days until mating | 3.0 ± 1.5 | 2.5 ± 1.2 | 2.8 ± 1.8 | 2.5 ± 1.5 |
| Mating Index, % | 95.8 (23/24) | 100 (24/24) | 100 (24/24) | 100 (24/24) |
| Fertility Index, % | 95.8 (23/24) | 95.8 (23/24) | 95.8 (23/24) | 95.8 (23/24) |

Reproductive parameters for female rats that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Pregnant rats | 23 | 23 | 23 | 23 |
| Corpora lutea/dam | 15.7 (361/23) | 15.5 (357/23) | 15.2 (335/23) | 15.3 (351/23) |
| Implantation sites/dam | 14.6 (336/23) | 14.5 (334/23) | 14.6 (321/23) | 14.3 (330/23) |
| Pre-implantation loss, % | 6.9 | 6.4 | 4.2 | 6.0 |
| Total resorbed or dead fetuses | 35 (10.4%) | 33 (9.9%) | 19 (5.9%) | 12 (3.6%) |
| Early resorbed or dead fetuses | 35 | 31 | 19 | 12 |
| Late resorbed or dead fetuses | 0 | 2 | 0 | 0 |
| Live fetuses/dam | 13.1 (301/23) | 13.1 (301/23) | 13.7 (302/23) | 13.8 (318/23) |
| Male/Female | 143/158 | 146/155 | 146/156 | 161/157 |
| Fetal body weight, g M/F | 3.50/3.31 | 3.49/3.26 | 3.50/3.27 | 3.59/3.41 |
| Placental weight, g | 0.51 | 0.47 | 0.48 | 0.50 |

5. Fetal Examinations: Fetal examinations revealed no treatment-related external, visceral, or skeletal malformation or variations; however, it should be noted that drug was not administered during the period of organogenesis. External anomalies were only observed for 3 (1.0%) fetuses at 3.2 mg/kg/day.

Visceral examination of $F_1$ fetuses from $F_0$ rats that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Number of fetuses examined | 145 | 140 | 148 | 153 |
| Unilateral anophthalmia | 0 | 0 | 0 | 1 (0.7%) |
| Unilateral microphthalmia | 0 | 0 | 0 | 1 (0.7%) |
| Dilatation of renal pelvis | 0 | 3 (2.1%) | 0 | 1 (0.7%) |
| Left umbilical artery | 0 | 0 | 0 | 2 (1.3%) |

Skeletal examination of $F_1$ fetuses from $F_0$ rats that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Number of fetuses examined | 156 | 158 | 154 | 165 |
| Wavy ribs | 0 | 1 (0.6%) | 0 | 1 (0.6%) |
| Shortened 13th rib | 0 | 2 (1.3%) | 1 (0.6%) | 1 (0.6%) |
| Variations of lumbar vertebrae | 0 | 1 (0.6%) | 1 (0.6%) | 5 (3.0%) |

In a Segment I study, the effect of omeprazole on fertility and reproductive performance were assessed in male and female Sprague-Dawley rats. Omeprazole was administered by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day. Male rats were treated with vehicle or omeprazole for 9 weeks prior to mating, during the mating period, and until the day prior to sacrifice. Female rats were treated with vehicle or omeprazole for 2 weeks prior to mating, during the mating period, and until day 7 of gestation. Omeprazole at doses ≤320 mg/kg/day had no effects on fertility or reproductive performance in rats. No listings were provided for individual animals.

Segment II Study: Intravenous Teratology Study with Omeprazole in Rats (Report No. R-249).

Testing Laboratory:

Date Started: May 12, 1989

Date Completed: March 9, 1990 (Translation from Japanese to English, June 12, 1998)

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies" and Yakuhatsu no. 870 (Pharmaceutical Affairs Bureau directive dated October 5, 1988), entitled "Amended regulations regarding pharmaceutical GLP and audits." A statement of compliance with the Quality Assurance Unit was included.

Animals: line rats At the start of treatment, female rats were 11 weeks old and the body weight range was 221-275 g.

Drug Batch: Omeprazole, Lot No. 14

Methods: In a Segment II teratology study, pregnant female Sprague-Dawley rats received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation. Controls received the vehicle,

. The sponsor's dose selection was based upon a 2-week dose range finding study in which omeprazole was administered by the intravenous route at doses of 10, 30, and 100 mg/kg/day. In the high dose group receiving 100 mg/kg/day, transient decreased spontaneous movements, tachypnea, and clonic convulsions were observed in both male and female rats immediately after dosing. Slight suppression of weight gain for male rats at 100 mg/kg/day was reported; although, it was not quantified. In the present study, there were 36 pregnant female rats/group with 24 dams for cesarean section on day 20 and 12 dams for natural delivery. Vehicle or drug solution was administered into the caudal vein at a dose volume of 3 mL/kg. During the treatment period, animals were monitored for clinical signs of toxicity and moribundity/mortality three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. At other periods of the

study, animals were monitored twice per day, once in the morning and once in the afternoon. $F_0$ dams were weighed daily on days 0, 3, 7-17, and 20 of gestation and on days 0, 4, 7, 11, 14, 17, and 21 of lactation. Food consumption was measured on days 1, 4, 8, 11, 14, 17, and 20 of gestation and on days 2, 4, 7, 11, 14, 17, and 21 of lactation. For pregnant $F_0$ female rats scheduled for cesarean section, animals were sacrificed on day 20 of gestation and autopsied. The ovaries and uterus were removed and the number of corpora lutea, number of implantations, number of viable fetuses, and number of dead and resorbed fetuses were determined. The ovaries were weighed. Placentas of viable fetuses were removed and weighed. Viable fetuses were examined for sex and external malformations or variations. Approximately, one-half of the viable fetuses were examined for visceral malformations and variations. Remaining fetuses were examined for skeletal malformations and variations. For pregnant $F_0$ female rats allowed to naturally deliver their offspring, the gestational period, number of live $F_1$ offspring births, and number of stillbirths were determined. Stillborn offspring were processed and subjected to visceral examination. $F_0$ female rats that did not deliver by day 24 of gestation were sacrificed and autopsied. Live $F_1$ offspring were examined for sex and external malformation, weighed, and then returned to $F_0$ dams. Live $F_1$ offspring were suckled by $F_0$ dams for up to 21 days after delivery. $F_0$ dams were sacrificed at 21 days postpartum and autopsied. The uterus was removed and the number of implantation scars were counted. $F_1$ pups were weighed twice per week up to day 21 postpartum and once a week from days 21 to 70. On day 4 postpartum, $F_1$ pups were randomly culled to make 4 pups/sex/litter. $F_1$ pups in excess of 8 per litter were sacrificed, fixed, and preserved. Development of $F_1$ pups was monitored as follows: opening of pinnae (days 4 and 7 postpartum), emergence of abdominal fur (days 7 and 11 postpartum), eruption of incisors (days 11 and 14 postpartum), opening of eyelids (days 14 and 17 postpartum), descent of testes (days 21 and 28 postpartum), and opening of vagina (days 35 and 42 postpartum). Survival of F1 pups was monitored daily from birth until day 70. $F_1$ pups that died during lactation were processed and subjected to visceral examination. $F_1$ pups that died after day 21 were autopsied and sites with anomalies were collected and preserved. Functional development of $F_1$ pups were assessed on day 21 postpartum as follows: righting reflex, pupillary reflex, pinna reflex, corneal reflex, and sense of hearing (Preyer's reflex). Behavioral development of two rats/sex/litter was assessed as follows: an open field test to study emotionality at 5 weeks postpartum; a water-filled multiple T-maze to study learning capacity at 7 weeks postpartum, and a shuttlebox test to study acquisition of the conditioned avoidance response at 9 weeks postpartum. $F_1$ rats used in behavioral tests as well as any remaining $F_1$ rats, not used in behavioral or reproductive capacity tests, were sacrificed at 10 to 12 weeks of age, autopsied, and abnormal sites were collected and preserved. Two $F_1$ rats/sex/litter were assessed for fertility and reproductive performance at 10 to 12 weeks of age. Pregnant $F_1$ female rats were weighed on days 0, 4, 8, 12, 16, and 20 of gestation and submitted to cesarean section on day 20 of pregnancy. After examinations as described in cesarean sections of the $F_0$ dams above, approximately one-half of the viable $F_2$ fetuses were fixed in Bouin's solution and remaining viable $F_2$ fetuses were fixed in 90% alcohol. $F_1$ male rats used in reproductive capacity studies were sacrificed after the mating period and autopsied. The testes, epididymides, prostates, seminal vesicles, and abnormal sites were collected and preserved.

**Results:**

1. Observed Effects for $F_0$ Dams: During the treatment period from days 7 to 17 of gestation, all $F_0$ dams at the high dose of 100 mg/kg/day were observed with clonic convulsions, tachypnea, and decreased spontaneous movements. A total of 15 animals in the high dose group were also observed with sporadic salivation during the treatment period (1-7 dams/days). All animals recovered by 1 hr after dosing and none of the observed effects noted above were found after the treatment period.

2. Mortality for $F_0$ Dams: None.

3. Body Weight and Food Consumption for $F_0$ Dams: Body weight gains of omeprazole-treated $F_0$ female rats from days 7 to 17 of gestation were unaffected. Body weights of $F_0$ female control rats on days 7 and 17 of gestation were 298.6 and 364.4 g, respectively. Body weight gains of $F_0$ female rats at 10, 3.2, and 100 mg/kg/day were 99.9, 98.7, and 102% of the control, respectively. Food consumption of $F_0$ female rats at 100 mg/kg/day from days 8 to 17 of gestation was reduced to 95.7% of the control (30.5 g/rat/day). Body weight gains and food consumption of $F_0$ female treatment groups from days 0 to 21 of lactation were unaffected as compared to the control.

4. Cesarean Section Data for $F_0$ Dams: For $F_0$ dams that received omeprazole by the intravenous route at doses of 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20, there were no treatment-related effects on the corpora lutea/dam, implantation sites/dam, pre-implantation loss, resorbed/dead fetuses, live fetuses/dam, male to female ratio, or fetal body weight. Placental weight was slightly decreased at the 100 mg/kg/day. There were no treatment-related gross pathological findings in $F_0$ dams. There were no treatment-related changes in absolute ovary weight. Female rats that were not pregnant were excluded from statistical analysis as follows: 3 female rats (1102, 1115, and 1117) of the control group, 1 animal (2104) of the 10 mg/kg/day group, 1 animal (3116) of the 32 mg/kg/day group, and 1 animal (4110) of the 100 mg/kg/day group.

Cesarean section data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # Female rats | 24 | 24 | 24 | 24 |
| # Not Pregnant | 3 | 1 | 1 | 1 |
| # Pregnant $F_0$ dams | 21 | 23 | 23 | 23 |
| Corpora lutea/dam | 17.1 (359/21) | 17.8 (409/23) | 17.0 (390/23) | 18.3 (421/23) |
| Implantation sites/dam | 15.5 (326/21) | 16.7 (384/23) | 15.3 (352/23) | 16.1 (371/23) |
| Pre-implantation loss, % | 9.2 (33/359) | 6.1 (25/409) | 9.7 (38/390) | 11.9 (50/421) |
| Resorbed/dead fetuses, %<br>-total<br>-early<br>-late | <br>6.1% (20/326)<br>5.8% (19/326)<br>0.3% (1/326) | <br>6.5% (25/384)<br>6.25% (24/384)<br>0.25% (1/384) | <br>5.1% (18/352)<br>4.8% (17/352)<br>0.3% (1/352) | <br>4.3% (16/371)<br>4.0% (15/371)<br>0.3% (1/371) |
| Live fetuses/dam | 14.6 (306/21) | 15.6 (359/23) | 14.5 (334/23) | 15.4 (355/23) |
| Male/Female Ratio | 1.13 (162/144) | 1.01 (180/179) | 0.95 (163/171) | 0.93 (171/184) |
| Fetal Body Weight, g<br>Male/Female | <br>3.71/3.58 | <br>3.74/3.54 | <br>3.77/3.50 | <br>3.69/3.43 |
| Placental Weight, g | 0.54 | 0.52 | 0.52 | 0.49* |

$p \leq 0.05$

5. External, Visceral, and Skeletal Malformations and Variations for $F_1$ Fetuses: There were no treatment-related external, visceral, or skeletal malformations or variations found in $F_1$ fetuses. There were no treatment-related effects on progress of ossification.

Visceral examinations of $F_1$ fetuses from $F_0$ dams that received omeprazole by the intravenous route at doses of 0, mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 147 | 176 | 162 | 170 |
| Situs inversus totalis | 0 | 0 | 1 (0.6%) | 1 (0.6%)[a] |
| Thymic remnant in neck | 7 (4.8%) | 8 (4.5%) | 10 (6.2%) | 17 (10.0%) |
| Interventricular septal defect | 0 | 0 | 0 | 1 (0.6%) |
| Abnormal lobation of liver | 1 (0.7%) | 1 (0.6%) | 3 (1.9%) | 2 (1.2%) |
| Left umbilical artery | 1 (0.7%) | 1 (0.6%) | 0 | 3 (1.8%) |

a. Associated with cardia bifida.

Skeletal examinations of $F_1$ fetuses from $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 158 | 182 | 172 | 183 |
| Cervical rib (V) | 2 (1.3%) | 3 (1.6%) | 3 (1.7%) | 5 (2.7%) |
| Shortened 13th rib (V) | 1 (0.6%) | 1 (0.5%) | 2 (1.2%) | 9 (4.9%) |
| Sacralization of lumbar vertebra (V) | 0 | 0 | 2 (1.2%) | 3 (1.6%) |
| Reduced ossification of pubis | 0 | 0 | 1 (0.6%) | 0 |
| # Ossified Metatarsus<br>-Left<br>-Right | <br>4.10<br>4.12 | <br>4.10<br>4.12 | <br>4.08<br>4.10 | <br>4.02*<br>4.04 |

6. Reproductive Data for $F_0$ Dams Allowed to Deliver Their Offspring: For $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation and were allowed to deliver there offspring, there were no treatment-related effects on the gestation period, implantation sites/dam, number of stillborn $F_1$ pups, live $F_1$ pups/dam, the male to female ratio, or live birth index. At doses of 0, 10, 32, and 100 mg/kg/day, there were 18, 10, 15, and 11 missing $F_1$ pups, respectively, which were not accounted for in data tables based upon total numbers of implantation sites and live fetuses. For visceral examinations of stillborn $F_1$ pups, thymic remnant in neck at doses of 0, 10, 32, and 100 mg/kg/day was found with an incidence of 0, 5 (55.6%), 1 (33.3%), and 2 (33.3%), respectively. Animals that did deliver by day 24 of pregnancy were sacrificed and autopsied as follows: 1 animal (1134) of the control group, 1 animal (3132) of the 32 mg/kg/day group, and 1 animal (4135) of the 100 mg/kg/day did not deliver by day 24 of pregnancy. There were no treatment-related gross pathological findings in $F_0$ dams sacrificed on day 21 postpartum.

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 11 | 12 | 12 | 11 |
| #$F_0$ dams that delivered pups[a] | 11 | 12 | 11 | 11 |
| Gestation period, days | 21.9 | 21.8 | 22.0 | 22.0 |
| Implantation sites/dam | 16.3 (179/11) | 15.8 (189/12) | 16.6 (183/11) | 15.0 (165/11) |
| Stillborn $F_1$ pups (%) | 3 (1.9%) | 9 (5.0%) | 3 (1.8%) | 6 (3.9%) |
| Missing pup-unaccounted[b] | 18 | 10 | 15 | 11 |
| Live $F_1$ pups/dam | 14.4 (158/11) | 14.2 (170/12) | 15.0 (165/11) | 13.5 (148/11) |
| Male to Female Ratio | 0.95 (77/81) | 1.13 (90/80) | 1.14 (88/77) | 0.90 (70/78) |
| Live birth index, % | 88.3 (158/179) | 89.9 (170/189) | 90.2 (165/183) | 89.7 (148/165) |

a. Status of dams that did not deliver was not given.
b. Missing pups = implantations - live pups - stillborn pups.

7. Viability and Development of $F_1$ Pups: There were no treatment-related effects on $F_1$ pup viability on days 4, 21, and 70. There were treatment-related effects on $F_1$ pup body weight or body weight gain from day 0 to 70 postpartum. There were no treatment-related gross pathological findings of $F_1$ fetuses culled on day 4. For the 0, 10, 32, and 100 mg/kg/day groups, visceral examination of 10, 8, 3, and 0 pups that died, respectively, revealed no treatment-related findings.

Viability and body weights for $F_1$ fetuses from $F_0$ dams that received omeprazole by the intravenous route at doses of 0, mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Viability of $F_1$ pups | | | | |
| Day 4 survival index, % | 91.8 (145/158) | 94.7 (161/170) | 97.6 (161/165) | 98.6 (146/148) |
| Day 21 weaning index, % | 98.8 (85/86) | 97.9 (94/96) | 97.7 (86/88) | 100 (88/88) |
| Day 70 viability Index, % | 100 (85/85) | 98.9 (93/94) | 100 (86/86) | 100 (88/88) |
| Body weight of $F_1$ pups, g (Male/Female) | | | | |
| Day 0 | 6.4/6.0 | 6.2/5.8 | 6.3/5.9 | 6.4/6.0 |
| Day 4 | 8.8/8.5 | 8.9/8.3 | 8.8/8.2 | 9.7/9.0 |
| Day 21 | 45.7/45.0 | 45.1/42.2 | 47.0/43.8 | 49.6/47.7 |
| Day 70 | 403.0/249.8 | 397.7/246.3 | 391.7/243.6 | 414.1/247.8 |

**Physical Development:** There were no treatment-related effects on physical development of $F_1$ pups (i.e., no effect on pinna detachment, appearance of abdominal hair, opening of vagina, eruption of lower incisor, opening of eyelid, or descent of testis).

**Functional Development:** There were no treatment-related effects on functional development of $F_1$ pups at weaning (i.e., no effects on righting reflex, pupillary reflex, pain response, corneal reflex, pinna reflex, or Preyer's reflex).

**Behavioral Development:** $F_1$ pups were submitted to an open field test to study behavior at 5 weeks postpartum, a water-filled multiple maze test to study learning capacity at 7 weeks postpartum, and a shuttlebox test to study acquisition of the conditioned avoidance response at 9 weeks postpartum. There were sporadic changes in the open field test and conditioned avoidance response for omeprazole-treatment groups that appeared to have little biological significance. $F_1$ pups used in behavioral tests were sacrificed at 10-12 weeks. Gross pathological examination found atrophy and softening of the testes and epididymides, bilaterally, in 2 males (9.5%) at 100 mg/kg/day.

Open Field Test: In the first test, no significant changes were observed in male or female treatment groups. In the second test, latency for $F_1$ male rats at doses of 32 and 100 mg/kg/day were increased to 222.5 and 318.9% of the control (11.1 sec); although changes were not statistically significant. Grooming for $F_1$ male rats at doses of 32 and 100 mg/kg/day was decreased to 46.1 and 53.8% of the control (1.3), respectively. Urination at doses of 10, 32, and 100 mg/kg/day was increased to 0.2, 0.3, and 0.2, respectively, as compared to 0.0 for the control. In the second test, latency for $F_1$ female rats at doses of 10, 32, and 100 mg/kg/day were increased to 394, 155, and 159.7% of the control (6.7 sec), respectively; although, changes were not statistically significant and tnere was not a dose response relationship.

Water-Filled Multiple Maze Test: No treatment-related effects were observed for either $F_1$ male or female rats.

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies." A statement of compliance with the Quality Assurance Unit was included.

Animals: line rats were used in this study. Female rats were 11 weeks old and had a body weight of 208-260 g prior to the start of the mating with male rats (untreated).

Drug Batch: Omeprazole, Lot No. 124

Methods: In a Segment II teratology study, pregnant female Sprague-Dawley rats received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation. Control animals received the vehicle, . The sponsor's selection of doses was based upon a 2-week oral dose range finding study with doses of 32, 100, 320, and 1000 mg/kg/day. A dose of 320 mg/kg/day was associated with suppression of body weight gain; although, the percent suppression was not provided. In the present study, there were 36 pregnant female rats/group: 24/group for cesarean section on day 20 and 12/group for natural delivery. The dose volume was 5 mL/kg. Rats were observed for clinical signs of toxicity and morbundity/mortality, three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. Body weights of $F_0$ female rats were measured on days 0, 3, 7-17, and 20 of gestation and on days 0, 4, 7, 11, 14, 17, and 21 of lactation. Food consumption was measured on days 1, 4, 8, 11, 14, 17, and 20 of gestation and on days 2, 4, 7, 11, 14, 17, and 21 of lactation. On day 20 of gestation, 24 pregnant female rats/group were scheduled for cesarean section. Following autopsy, the ovaries and uterus were removed and the number of corpora lutea, number of implantations, number of viable fetuses, and number of dead and resorbed fetuses were determined. The placentas were removed and weighed. The pre-implantation loss and percentage of dead and resorbed fetuses were calculated. For viable fetuses, sex and body weight were determined and examinations were conducted to identify any external malformations. Approximately one-half of the viable fetuses of each litter were examined for visceral malformations and variations. The remaining viable fetuses were examined for skeletal malformations, skeletal variations, and ossification progress. Twelve pregnant female $F_0$ dams per group were allowed to deliver their offspring. The delivery status was observed and the gestational period and birth index were calculated. Dams that did not deliver by day 24 of pregnancy were sacrificed, autopsied, the contents of the uterus were examined, and all data for animals determined to be infertile was excluded. For $F_1$ pups, the number of live births, number of stillbirths, external anomalies, weight, and sex were determined on the day of delivery. The lactation condition (i.e., suckling) was monitored over 21 days postpartum. $F_0$ dams were sacrificed on day 21 postpartum, autopsied, and the uteri were removed to determine the number of implantation sites (i.e., scars). $F_1$ pups were weighed twice per week until day 21 postpartum and once per week from days 21 to 70. After $F_1$ pups were weighed on day 4 postpartum, litters were randomly culled to 4 pups/sex/litter, when possible.

For $F_1$ pups, viability, development (i.e., physical, functional, and behavioral), and fertility and performance were assessed as described earlier in methods for Report No. R-249.

**Results:**

**1. Observed Effects for $F_0$ Dams:** At the high dose of 320 mg/kg/day, salivation was observed for 3 to 5 animals/day immediately after dosing from days 13 to 17 of gestation. A total of 11 animals were observed with salivation after dosing during this period. This effect was not observed after the discontinuation of dosing.

**2. Mortality for $F_0$ Dams:** None.

**3. Body Weight and Food Consumption for $F_0$ Dams:** Body weight gain was suppressed by >10% for $F_0$ dams at the high dose of 320 mg/kg/day from days 7 to 17 of gestation (i.e., treatment period). Body weights for control $F_0$ dams on days 7 and 17 of gestation were 280.5 and 338.6 g, respectively. Body weight gains for $F_0$ dams at 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation were 108, 107.4, and 75.3% of the control, respectively. Food consumption for $F_0$ dams at 320 mg/kg/day on days 8, 11, 14, and 17 of gestation was reduced to 90% of the control (25.9 g/rat/day). Body weight gains and food consumption of $F_0$ dams in omeprazole treatment groups from days 0 to 21 of lactation were unaffected as compared to the control group.

**4. Cesarean Section Data for $F_0$ Dams:** For $F_0$ dams that received omeprazole by the oral route at doses of 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20, there were no treatment-related effects on corpora lutea/dam, implantation sites/dam, pre-implantation loss, resorbed/dead fetuses, live fetuses/dam, the male to female ratio, or fetal body weight. Placental weight was significantly decreased at the 320 mg/kg/day.

Cesarean section data for $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Pregnant $F_0$ dams | 24 | 24 | 24 | 22[a] |
| Corpora lutea/dam | 16.2 (388/24) | 16.7 (401/24) | 16.1 (386/24) | 17.0 (373/22) |
| Implantation sites/dam | 15.0 (361/24) | 15.5 (373/24) | 15.1 (362/24) | 15.9 (350/22) |
| Pre-implantation loss, % | 7% (27/388) | 7% (28/401) | 6.2% (24/386) | 6.2% (23/373) |
| Resorbed/dead fetuses<br>-total<br>-early<br>-late | <br>24/361 (6.6%)<br>23<br>1 | <br>25/373 (6.7%)<br>24<br>1 | <br>29/362 (8.0%)<br>28<br>1 | <br>32/350 (9.1%)<br>32<br>0 |
| Live fetuses/dam | 14.0 (337/24) | 14.5 (348/24) | 13.9 (333/24) | 14.5 (318/24) |
| Male/Female Ratio | 0.97 (166/171) | 0.97 (171/177) | 0.95 (162/171) | 1.00 (159/159) |
| Fetal Body Weight, g<br>Male/Female | <br>3.64/3.46 | <br>3.72/3.54 | <br>3.59/3.38 | <br>3.63/3.43 |
| Placental Weight, g | 0.53 | 0.51 | 0.50 | 0.49[b] |

a. The sponsor did not account for 2 $F_0$ dams at the high dose of 320 mg/kg/day that appear to be missing.
b. $p \leq 0.05$.

5. External, Visceral, and Skeletal Malformations and Variations for $F_1$ Fetuses: There were no treatment-related external, visceral, or skeletal malformations or variations found in $F_1$ fetuses. There were no treatment-related effects on progress of ossification.

Visceral examinations of $F_1$ fetuses from $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 164 | 167 | 159 | 153 |
| Dilatation of lateral ventricles | 0 | 0 | 3 (1.9%) | 0 |
| Unilateral anophthalmia | 0 | 1 (0.6%) | 0 | 0 |
| Thymic remnant in the neck | 16 (9.8%) | 9 (5.4%) | 12 (7.5%) | 24 (5.7%) |
| Diaphragmatocele | 0 | 1 (0.6%) | 3 (1.9%) | 0 |
| Dilatation of ureter | 0 | 0 | 2 (1.3%) | 0 |
| Left umbilical artery | 1 (0.6%) | 1 (0.6%) | 2 (1.3%) | 3 (2.0%) |

Skeletal examinations of $F_1$ fetuses from $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were submitted to cesarean section on day 20.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 172[a] | 181 | 174 | 165 |
| Hypoplasia ossification of thoracic vertebral body (V) | 0 | 0 | 1 (0.6%) | 0 |
| Shortened 13th rib (V) | 1 (0.6%) | 3 (1.7%) | 3 (1.7%) | 1 (0.6%) |
| Hypoplasia of ribs (V) | 0 | 0 | 1 (0.6%) | 0 |
| 14th rib (V) | 3 (1.7%) | 4 (2.2%) | 3 (1.7%) | 8 (4.8%) |

a. Lost 1 $F_1$ fetus.

6. Reproductive Data for $F_0$ Dams Allowed to Deliver Their Offspring: One dam (#4126) at 320 mg/kg/day did not deliver by day 24 of gestation. Autopsy findings for this dam revealed one viable fetus in the left uterine horn, one implantation scar in the right uterine horn, and nipple immaturity. For $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation and were allowed to deliver there offspring, there were no treatment-related effects on the gestation period, implantation sites/dam, number of stillborn $F_1$ pups, live $F_1$ pups/dam, the male to female ratio, or live birth index. There were no findings with skeletal examinations of stillborn $F_1$ pups. There were no treatment-related gross pathological findings in $F_0$ dams sacrificed on day 21 postpartum. At doses of 0, 3.2, and 32 mg/kg/day, there were 2, 6, and 6 missing $F_1$ pups, respectively, which were not accounted for in data tables.

Delivery data for $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 11 | 11 | 12 | 12 |
| # $F_0$ dams that delivered pups | 11 | 11 | 12 | 11 |
| Gestation period, days | 22.0 | 22.0 | 22.1 | 22.4 |
| Implants/dam | 14.3 (157/11) | 13.7 (151/11) | 14.8 (177/12) | 14.7 (162/11[a]) |
| Stillborn $F_1$ pups | 4 (2.6%) | 5 (3.4%) | 1 (0.6%) | 2 (1.2%) |
| Live $F_1$ pups/dam | 13.7 (151[b]/11) | 12.7 (140[b]/11) | 14.2 (170[b]/12) | 14.5 (160/11) |
| Male to Female Ratio | 0.99 (75/76) | 1.15 (75/65) | 0.93 (82/88) | 0.90 (76/84) |
| Live birth index, % | 96.2% (151/157) | 92.7% (140/151) | 96.0% (170/177) | 98.8% (160/162) |

a. One dam (#4126) at 320 mg/kg/day did not deliver by day 24 of gestation.
b. At doses of 0, 3.2, and 32 mg/kg/day, there were 2, 6, and 6 missing $F_1$ pups, respectively, which were not accounted for in data tables.

**7. Viability and Development of $F_1$ Pups:** There were no treatment-related effects on $F_1$ pup viability on days 4, 21, and 70. There were no treatment-related effects on $F_1$ pup body weight or body weight gain from day 0 to 70 postpartum. There were no treatment-related gross pathological findings of $F_1$ fetuses culled on day 4.

Viability and body weights for $F_1$ fetuses from $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Viability of $F_1$ pups | | | | |
| Day 4 survival index, % | 99.3 (150/151) | 99.3 (139/140) | 91.8 (156/170) | 100 (160/160) |
| Day 21 weaning index, % | 100 (88/88) | 100 (88/88) | 97.7 (86/88) | 98.9 (87/88) |
| Day 70 viability Index, % | 100 (88/88) | 100 (88/88) | 100 (86/86) | 100 (87/87) |
| Body weight of $F_1$ pups, g (Male/Female) | | | | |
| Day 0 | 6.2/5.9 | 6.2/5.9 | 6.0/5.7 | 6.4/6.1 |
| Day 4 | 9.3/8.9 | 9.9/9.5 | 9.4/9.1 | 9.6/9.3 |
| Day 21 | 44.2/42.2 | 45.7/43.9 | 41.9/41.2 | 43.4/42.1 |
| Day 70 | 376.6/240.4 | 393.5/251.5 | 378.7/241.8 | 383.4/238.8 |

**Physical Development:** There were no treatment-related effects on physical development of $F_1$ pups (i.e., no effect on pinna detachment, appearance of abdominal hair, opening of vagina, eruption of lower incisor, separation of eyelid, or descent of testis).

**Functional Development:** There were no treatment-related effects on functional development of $F_1$ pups at weaning (i.e., no effects on righting reflex, pupillary reflex, pain response, corneal reflex, pinna reflex, or Preyer's reflex).

**Behavioral and Learning Development:** $F_1$ pups were submitted to an open field test to study behavior at 5 weeks postpartum, a water-filled multiple maze test to study learning capacity at 7 weeks postpartum, and a shuttlebox test to study acquisition of the conditioned avoidance response at 9 weeks postpartum. $F_1$ pups used in behavioral tests were sacrificed at 10 weeks and no treatment-related gross pathological changes were found.

Open Field Tests for $F_1$ Male Rats: In the first test, ambulation of $F_1$ male rats at omeprazole doses of 3.2, 32, and 320 mg/kg/day were increased to 139.2, 144.9, and 188.6% of the control (15.8), respectively; although, only the change at 320 mg/kg/day was statistically significant. Defecation for $F_1$ male rats at doses of 32 and 320 mg/kg/day was increased to 133.3 and 146.7% of the control (1.3), respectively; although, changes were not statistically significant. Urination for $F_1$ male rats at 320 mg/kg/day was increased to 161.5% of the control (1.3), respectively; although, the change was not statistically significant. In the second test, ambulation of $F_1$ male rats at 32 and 320 mg/kg/day was increased to 198.9 and 180.3% of the control (18.3), respectively. Defecation for $F_1$ male rats at 3.2, 32, and 320 mg/kg/day was increased to 214.3, 185.7, and 300% of the control (0.7), respectively; although, only the change at 320 mg/kg/day was statistically significant. Urination for $F_1$ male rats at 3.2, 32, and 320 mg/kg/day was increased to 140, 160, and 260% of the control (0.5), respectively; although, only the change at 320 mg/kg/day was statistically significant.

Open Field Tests for $F_1$ Female Rats: In the first test, latency of $F_1$ female rats at doses of 32 and 320 mg/kg/day were decreased to 31.3 and 30% of the control (15.0 sec); although, changes were not statistically significant. Ambulation of $F_1$ female rats at omeprazole doses of 32 and 320 mg/kg/day were increased to 233.1 and 209.3% of the control (15.1), respectively. Rearing of $F_1$ female rats at doses of 32 and 320 mg/kg/day were increased to 133.85 and 169.2% of the control (6.5), respectively; although, only the change at 320 mg/kg/day was statistically significant. Grooming of $F_1$ female rats at doses of 32 and 320 mg/kg/day was increased to 183.3 and 200% of the control (0.6), respectively; although, only the change at 320 mg/kg/day was statistically significant. In the second test, latency of $F_1$ female rats at doses of 3.2, 32, and 32 mg/kg/day were decreased to 15.5, 29.9, and 21.6% of the control (9.7 sec), respectively; although, changes were not statistically significant. Ambulation of $F_1$ female rats at doses of 3.2, 32, and 320 mg/kg/day were increased to 171.4, 271.4, and 239.8% of the control (16.1), respectively; although, only changes at 32 and 320 mg/kg/day were statistically significant. Rearing of $F_1$ female rats at doses of 3.2, 32, and 320 mg/kg/day were increased to 171.8, 194.9, and 179.5% of the control (3.9); although, only the change at 32 mg/kg/day was statistically significant. Grooming of $F_1$ female rats in all omeprazole treatment groups were increased to 200% of the control (0.4); although, changes were not statistically significant. Urination of $F_1$ female rats in omeprazole treatment groups were increased to 150-200% of the control (0.4); although, changes were statistically significant.

Water-filled Multiple Maze Test: No treatment-related changes were found in $F_1$ male or female rats in water-filled multiple maze tests with regard to elapsed times or counts of errors.

Conditioned Avoidance Response in $F_1$ Male Rats: Percent avoidance response values were generally decreased in $F_1$ male rats at 32 and 320 mg/kg/day as compared to the control. In Session 4, the percent avoidance response values of $F_1$ male rats at 32 and 320 mg/kg/day were decreased to 62.6 and 72.7% of the control (56.7%), respectively; although, only the change at 32 mg/kg/day was statistically significant. In Session 5, the percent avoidance response values of $F_1$ male rats at 32 and 320 mg/kg/day were decreased to 64.2 and 61.2% of the control (66.2%), respectively. In the first

trial, the percent non-escape response of $F_1$ male rats at 320 mg/kg/day was increased to 866.7% of the control (0.3). Latency values for $F_1$ male rats at 32 and 320 mg/kg/day were generally increased as compared to control. In trial 3, the latency values for $F_1$ male rats at 32 and 320 mg/kg/day were increased to 127.6 and 119.3% of the control (3.48 sec), respectively; although, only the change at 32 mg/kg/day was statistically significant. In trial 4, the latency values for $F_1$ male rats at 32 and 320 mg/kg/day were increased to 126.1 and 116.8% of the control (3.45 sec), respectively; although, only the change at 32 mg/kg/day was statistically significant. In trial 5, the latency values for $F_1$ male rats at 32 and 320 mg/kg/day were increased to 135.8 and 132.1% of the control (2.99 sec), respectively.

Conditioned Avoidance Response in $F_1$ Female Rats: There were no treatment-related changes in percent avoidance response, percent no-escape response, or latency for $F_1$ female rat groups.

8. **Fertility and Reproductive Performance of $F_1$ Rats:** There were no treatment-related effects on fertility and reproductive performance of $F_1$ male and female rats. Mating and fertility indexes were unaffected. Body weight gains and food consumption of $F_1$ dams during gestation were unaffected. There were no treatment-related effects on corpora lutea/dam, implantation sites/dam, pre-implantation loss, resorbed or dead fetuses, number of live fetuses/dam, male to female ratio, $F_2$ fetal body weight, or placental weight. No external malformations were evident in $F_2$ fetuses. Gross pathological examination of $F_1$ male rats used in reproductive tests found dilatation of renal pelvis for 1 (3.2%) male at 3.2 mg/kg/day, 0 at 32 mg/kg/day, and 2 (9.1%) males at 320 mg/kg/day as compared to 0 for the control. Absolute and relative testes weights of $F_1$ male rats were unaffected.

In a Segment II teratology study, pregnant female Sprague-Dawley rats received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation. There were 36 pregnant female rats/group: 24/group for cesarean section on day 20 and 12/group for natural delivery. Omeprazole was not teratogenic in rats at oral doses ≤320 mg/kg/day; however, toxic effects on behavioral development were evident. There were no treatment-related external, visceral, or skeletal malformations or variations found in $F_1$ fetuses. Body weight gain for $F_0$ dams at 320 mg/kg/day during the treatment period from days 7 to 17 of gestation was suppressed to 75.3% of the control. For $F_0$ dams allowed to deliver their offspring, reproductive parameters were unaffected; although, one dam at 320 mg/kg/day did not deliver by day 24 of gestation. There were no treatment-related effects on $F_1$ pup viability, body weight gain, physical development, or functional development. With regard to behavioral development, potential treatment-related changes were observed with $F_1$ rats in the open field test and conditioned avoidance response, but not in the water-filled multiple maze test. In open field tests with $F_1$ male rats, ambulation was increased for all treatment groups. Defecation and urination were increased for $F_1$ male rats at 32 and 320 mg/kg/day. In open field tests with $F_1$ female rats, ambulation, rearing, and grooming were increased at 32 and 320 mg/kg/day. Latency was decreased in all $F_1$ female treatment groups. For the conditioned avoidance response, low avoidance index values and prolonged latency were observed for $F_1$ male rats at 32 and 320 mg/kg/day; although, no changes were observed for $F_1$ female rats. There

were no treatment-related effects on fertility and reproductive performance for $F_1$ male or female rats. Body weight gains of $F_1$ dams during gestation were unaffected. Reproductive parameters for $F_1$ dams were unaffected. No treatment-related external malformations were evident in $F_2$ fetuses. No listings were provided for individual animals. The sponsor did not account for the pregnancy status in all $F_0$ female rats. For $F_0$ dams allowed to deliver their offspring, the sponsor did not account for all $F_1$ pups.

Rabbit

Segment II Study: Intravenous Teratology Study in Rabbits (Report No. R-399).

Testing Laboratory:

Date Started: July 10, 1991

Date Completed: March 31, 1992 (Translation from Japanese to English, June 15, 1998)

GLP Regulations: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies" and Yakuhatsu no. 870 (Pharmaceutical Affairs Bureau directive dated October 5, 1988), entitled "Amended regulations regarding pharmaceutical GLP and audits." A statement of compliance with the Quality Assurance Unit was included.

Animals: Pregnant female New Zealand white ( rabbits were used in this study. On day 0 of gestation, pregnant female rabbits were approximately 17 weeks old and had a body weight range of 3.11-4.19 kg.

Drug Batch: Omeprazole sodium, Lot No. J

Methods: In a Segment II teratology study, pregnant female rabbits received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation. Control animals received the vehicle, . Dose selection was based upon two intravenous dose range finding studies (Report No. R-306, February 20, 1991). In the first dose range finding study, non-pregnant female rabbits received omeprazole by the intravenous route at doses of 10, 32, and 100 mg/kg/day for 7 days. All animals that received 100 mg/kg/day died within 24 hr after the first treatment. Decreased weight gain and food consumption were observed at doses of 10 and 32 mg/kg/day; although, no control group was included in the study for comparison. In the second dose range finding study, pregnant female rabbits received omeprazole by the intravenous route at doses of 0, 1, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation. Body weights for the 10 and 32 mg/kg/day groups on day 18 were reduced by 1.24 and 2.75%,

respectively, relative to values at the start of treatment on day 6. Food consumption during the treatment period for the 10 and 32 mg/kg/day groups were reduced to 78.5 and 65.3% of the control (129.92 g/rabbit/day), respectively. There were no treatment-related changes with regard to the number of corpora lutea/dam, number of implantation sites/dam, pre-implantation loss, percentage of dead/resorbed fetuses, number of viable fetuses/dam, sex ratio, and placenta weights. In the present study, there were 16 pregnant female rabbits per group. Vehicle or drug solution was administered at a dose volume of 3 mL/kg into a vein of the ear once per day. During the treatment period, animals were observed for clinical signs of toxicity, existence of spontaneous abortions, and moribundity/mortality three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. At other times of the study, animals were observed twice per day, once in the morning and once in the afternoon. Body weights were measured on days 0, 6 to 20, 22, 24, 26, and 28 of gestation. Food consumption was measured on days 6 to 20, 22, 24, 26, and 28 of gestation. Animals were sacrificed on day 28 of gestation and submitted to a gross pathological examination. The ovaries and uteri were removed and the number of corpora lutea were counted. In the uterus, the number of implantation sites, viable fetuses, and dead/resorbed fetuses were determined. Animals that aborted were weighed and submitted to gross pathological examination as described above. Dead/resorbed fetuses and any organs with abnormalities were collected and preserved. Viable fetuses and as many dead fetuses as possible were examined for external malformations. For viable fetuses, body weight and placenta weight were measured. Viable fetuses were processed for determination of sex. Approximately one-half of the viable fetuses were examined for visceral malformations and variations. Remaining fetuses were examined for skeletal malformations and variations as well as the progress of ossification.

Results:

1. Observed Effects: Spontaneous abortions occurred for 1 animal (3102) at 10 mg/kg/day on day 20 of gestation and 1 animal (4114) at 32 mg/kg/day on day 27 of gestation. For the 1 animal at 10 mg/kg/day that aborted, food consumption was decreased from day 12 of gestation and body weight decreased from day 17 of gestation. For the 1 animal at 32 mg/kg/day that aborted, stool output decreased from day 11 of gestation, weight loss developed after the start of treatment on day 6 of gestation, and there was little to no food consumption from day 11 to day 27, when abortion occurred. The sponsor attributed decreased food consumption as the probable cause of abortions in these 2 animals; although, food consumption was decreased by >15% in all omeprazole-treatment groups as noted below. Decreased stool output was observed temporarily or persistently in all treatment groups. Two animals (2103 and 2133) at 3.2 mg/kg/day were observed with decreased stool output on days 17 to 20 of gestation. Three animals (3104, 3106, and 3113) at 10 mg/kg/day were observed with decreased stool output on days 13 to 21 and day 27 of gestation. Six animals (4103, 4106, 4111, 4112, 4114, and 4115) at 32 mg/kg/day were observed with decreased stool output on days 8 to 26 of gestation.

2. Mortality: None.

3. Body Weight and Food Consumption: Body weight losses were observed in all treatment groups from days 6 to 18 of gestation. Body weights for female controls on days 6 and 18 of gestation were 3.74 and 3.84 kg, respectively, yielding a 2.7% increase of body weight on day 6. Pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation lost 0.5, 1.9, and 4.6% of body weight on day 6, respectively. Food consumption for pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation was decreased to 82.6, 73.5, and 58.1% of the control (143.4 g/rabbit/day), respectively.

4. Cesarean Section Data for $F_0$ Dams: For pregnant female rabbits that received omeprazole by the intravenous route at a dose of 32 mg/kg/day from days 6 to 18 of gestation and were submitted to cesarean section on day 28, the pre-implantation loss was increased to 23.1% as compared to 15.1% for the control. Consequently, live fetuses/dam at 32 mg/kg/day were decreased to 7.5 as compared to 8.9 for the control. Implantation sites/dam at 32 mg/kg/day were decreased to 7.7 as compared to 9.0 for controls. No changes were found for corpora lutea/dam, resorbed/dead fetuses, the male to female ratio, fetal body weight, and placental weight.

Cesarean section data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation and were sacrificed on day 28 of gestation.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day |
|---|---|---|---|---|
| Total number of rabbits | 16 | 16 | 16 | 16 |
| Non-pregnant rabbits | 1 | 0 | 0 | 2 |
| Aborted | 0 | 0 | 1 | 1 |
| Pregnant Rabbits | 15 | 16 | 15 | 13 |
| Corpora lutea/dam | 10.6 (159/15) | 10.5 (168/16) | 10.9 (164/15) | 10.0 (130/13) |
| Implantation sites/dam | 9.0 (135/15) | 8.6 (137/16) | 9.0 (135/15) | 7.7 (100/13) |
| Pre-implantation loss, % | 15.1 (24/159) | 18.5 (31/168) | 17.7 (29/164) | 23.1 (30/130) |
| Resorbed/dead fetuses<br>-total<br>-early<br>-late | <br>2 (1.5%)<br>1<br>1 | <br>11 (8.0%)<br>5<br>6 | <br>11 (8.1%)<br>5<br>6 | <br>3<br>0<br>3 |
| Live fetuses/dam | 8.9 (133/15) | 7.9 (126/16) | 8.3 (124/15) | 7.5 (97/13) |
| Male/Female Ratio | 0.93 (64/69) | 0.94 (61/65) | 0.97 (61/63) | 0.80 (43/54) |
| Fetal Body Weight, g<br>Male/Female | <br>36.87/36.02 | <br>35.63/35.72 | <br>35.31/32.80 | <br>34.54/34.97 |
| Placental Weight, g | 3.30 | 3.53 | 3.46 | 3.44 |

5. Gross Pathological Examination of Pregnant Female Rabbits After Cesarean Section: Disseminated red spots were observed in the stomach for all treatment groups; although, the incidence did not display a dose response relationship. For the dam at 32 mg/kg/day that aborted on day 27, pale coloration of the liver and retention of a fur ball in the stomach were found. For the dam at 10 mg/kg/day that aborted on day 20, a blood-like substance was found adhering around the anus; although, there were no gross pathological findings in major organs in the thoracic or abdominal cavities.

Gross pathological findings for pregnant female rabbits that received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation.

| Organ/Tissue | 0 mg/kg/day | 3.2 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day |
|---|---|---|---|---|
| #Dams examined | 15 | 16 | 16[a] | 14[b] |
| Stomach | | | | |
| -disseminated red spots | 0 | 1 | 2 | 1 |
| -retention of fur mass | 0 | 0 | 0 | 1 |
| Liver | | | | |
| -pale in color | 0 | 0 | 0 | 1 |

a. 1 dam aborted on day 20 of gestation.
b. 1 dam aborted on day 27 of gestation.

**6. External, Visceral, and Skeletal Malformations and Variations for $F_1$ Fetuses:** Fusion of the sternebrae, a skeletal malformation, was observed for 1 fetus (1.6%) at 10 mg/kg/day and 1 fetus (2.1%) at 32 mg/kg/day; although, these findings appear to fall within the background incidence. The background incidence of fused sternebrae is 0.92 ± 1.45% with a range of 0 to 8.54 (MARTA Historical Control Project, New Zealand White Rabbits from the Years 1989 to 1992, Handbook of Developmental Toxicology. Editor: R.D. Hood. CRC Press, New York, 1997, page 728). The incidence of fetuses with a 13th rib, a skeletal variation, was increased at 32 mg/kg/day. There were no external or visceral malformations or variations.

Visceral examinations of $F_1$ fetuses from pregnant female rabbits that received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation and were submitted to cesarean section on day 28.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 67 | 63 | 62 | 49 |
| Thymic remnant in neck (V) | 0 | 2 (3.2%) | 0 | 0 |
| Variation of aortic arch | | | | |
| Type 4 | 8 (11.9%) | 16 (25.4%) | 12 (19.4%) | 18 (36.7%) |

Skeletal examinations of $F_1$ fetuses from pregnant female rabbits that received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation and were submitted to cesarean section on day 28.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ fetuses examined | 66 | 63 | 62 | 48 |
| Fusion of sternebrae (M) | 0 | 0 | 1 (1.6%) | 1 (2.1%) |
| Number of fetuses with 13th rib (V) | | | | |
| -right | 2 (3.0%) | 4 (6.3%) | 4 (6.5%) | 0 |
| -left | 2 (3.0%) | 4 (6.3%) | 5 (8.1%) | 1 (2.1%) |
| -bilateral | 42 (63.6%) | 44 (69.8%) | 38 (61.3%) | 42 (87.5%) |
| -total | 46 (69.7%) | 52 (82.5%) | 47 (75.8%) | 43 (89.6%*) |

$p \leq 0.05$

In a Segment II teratology study, pregnant female rabbits received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation. Omeprazole at intravenous doses ≤ 32 mg/kg/day was not teratogenic in rabbits. Fusion of the sternebrae, a skeletal malformation, was observed for 1 fetus (1.6%) at 10 mg/kg/day and 1 fetus (2.1%) at 32 mg/kg/day; although, these findings appear to fall within the background incidence. Spontaneous abortions occurred for 1 animal at 10 mg/kg/day on day 20 of gestation and 1 animal at 32 mg/kg/day on day 27 of gestation. The sponsor attributed decreased food consumption as the probable cause of abortions in these 2 animals; although, food consumption was decreased by >15% in all omeprazole-treatment groups. The pre-implantation loss at 32 mg/kg/day was increased to 23.1% as compared to 15.1% for the control. Consequently, live fetuses/dam at 32 mg/kg/day were decreased to 7.5 as compared to 8.9 for the control. Implantation sites/dam at 32 mg/kg/day were decreased to 7.7 as compared to 9.0 for controls. Pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation lost 0.5, 1.9, and 4.6% of body weight on day 6, respectively. Food consumption for pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation was decreased to 82.6, 73.5, and 58.1% of the control (143.4 g/ rabbit/day), respectively.

Rat

Segment III Study: Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Intravenous Route (Report No. R-361).

Testing Laboratory:

Date Started: April 12, 1991

Date Completed: February 20, 1992 (Japanese to English Translation, June 15, 1998)

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies" and Yakuhatsu no. 870 (Pharmaceutical Affairs Bureau directive dated October 5, 1988), entitled "Amended regulations regarding pharmaceutical GLP and audits." A statement of compliance with the Quality Assurance Unit was included.

Animals: Pregnant female line rats were used in the present study, On day 0 of gestation, animals were approximately 11 weeks of age and the body weight range was 227-328 g.

Drug Batch: Omeprazole Sodium, Lot No. J

Methods: In a Segment III perinatal and postnatal development study, pregnant $F_0$ female Sprague-Dawley rats received omeprazole by the intravenous route of administration at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum. Controls received the vehicle, [redacted]. There were 24 pregnant $F_0$ female rats per group. Vehicle or drug solution was administered into veins of the tail using a dose volume of 3 mL/kg. During the treatment period, $F_0$ dams were monitored for clinical signs of toxicity three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. During other periods, animals were monitored twice per day, one in the morning and once in the evening. Body weights were measured on days 0, 4, 7, 11, and 14 of gestation, days 17 to delivery, and days 0, 2, 4, 7, 11, 14, 17, and 21 postpartum. Food consumption was measured on days 1, 4, 8, 11, 14, 17, and 20 of gestation and days 2, 4, 7, 11, 14, 17, and 21 postpartum. $F_0$ dams were allowed to deliver their offspring. The suckling status of $F_0$ dams was observed for 21 days postpartum. $F_0$ dams that did not deliver by 24 of gestation were sacrificed and subjected to gross pathological examination. On day 22 postpartum, $F_0$ dams were sacrificed and submitted to gross pathological examination. Uteri were removed and the number of implantation scars were counted. For $F_1$ offspring, the numbers of live births and stillbirths were counted. Each $F_1$ offspring was examined for external malformations, sex was determined, and body weight was measured. $F_1$ pups were weighed twice per week until day 21 postpartum and once per week from days 21 to 70 postpartum. On day 4 postpartum, $F_1$ pups were randomly selected to make 4 pups/sex/litter. For $F_1$ pups, viability, development (i.e., physical, functional, and behavioral), and fertility and performance were assessed as described earlier in methods for Report No. R-249.

Results:

1. Observed Effects: For $F_0$ dams at 100 mg/kg/day, transient decreases in spontaneous movement, tachypnea, and clonic convulsions were observed immediately after dosing in all animals throughout the administration period. Prone position was also observed in all animals immediately after dosing from day 17 of gestation onward, but had was no longer found by day 8 postpartum. These observed effects had dissipated by 1 hr after dosing. Swelling and necrosis of the tail were observed in 3 $F_0$ dams at 100 mg/kg/day from day 4 postpartum to the end of treatment.

2. Mortality: None.

3. Body Weight and Food Consumption: Body weight gains of $F_0$ dams at 32 and 100 mg/kg/day from days 17 to 20 of gestation were slightly impaired; however, no impairment of body weight gain was evident for treatment groups from day 0 to 21 postpartum. Body weights of female controls on days 17 and 21 of gestation were 392.2 and 439.6 g, respectively. Body weight gains of $F_0$ dams at 10, 32, and 100 mg/kg/day from days 17 to 20 of gestation were 96.6, 89.8, and 88.9% of the control, respectively. Food consumption for $F_0$ dams at 100 mg/kg/day from days 17 to 20 of gestation was

reduced to 92.2% of the control (31.9 g/rat/day). Body weights of female controls on days 0 and 21 postpartum were 331.7 and 352.9 g, respectively. Body weight gains of $F_0$ dams from days 0 to 21 postpartum were 120.8, 106.5, and 129.1% of the control, respectively. Food consumption for $F_0$ dams at 32 and 100 mg/kg/day from days 0 to 21 postpartum were 93.5 and 91.4% of the control (61.7 g/rat/day), respectively.

**4. Reproductive Data for $F_0$ Dams:** Live pups/dam at 10, 32, and 100 mg/kg/day were reduced to 93, 91.1, and 89.2% of the control (15.7 live pups/dam), respectively. The live birth index (number of live birth/number of implantations) was reduced at 10, 32 and 100 mg/kg/day; although, changes were only significant at 32 and 100 mg/kg/day. Based upon numbers of implantation sites, live born, and stillborn at 0, 10, 32, and 100 mg/kg/day, the sponsor did not account for 10, 21, 18, and 27 fetuses, respectively.

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 24 | 24 | 24 |
| # $F_0$ dams that delivered liver pups | 24 | 23 | 23 | 24 |
| Gestation period (days) | 22.4 | 22.3 | 22.4 | 22.3 |
| Implantations/dam | 16.5 (396/24) | 16.0 (369/23) | 15.6 (359/23) | 15.8 (378/24) |
| Live $F_1$ pups/dam | 15.7 (376/24) | 14.6 (335/23) | 14.3 (330/23) | 14.0 (335/24) |
| Live Birth Index,% | 94.9% (376/396) | 90.8% (335/369) | 91.9%* (330/359) | 88.6%* (335/378) |
| Stillborn pups (%) | 10 (2.6%) | 13 (3.7%) | 11 (3.2%) | 16 (4.6%) |
| Unaccounted pups | 10 | 21 | 18 | 27 |
| Male/Female Ratio | 0.97 (185/191) | 1.13 (178/157) | 0.92 (159/172) | 1.09 (175/160) |
| Fetal body weight, g Male/Female | 6.7/6.3 | 6.8/6.4 | 6.9/6.4 | 6.6/6.3 |

$p \leq 0.05$

**5. Gross Pathological Examination of $F_0$ Dams:** At injection sites in the tail, three (14.3%) $F_0$ dams at 100 mg/kg/day were observed with necrosis. One (4.8%) of these dams was also observed with swelling. Necrosis was attributed to a local irritant effect of omeprazole at the injection site.

**6. Viability and Development of $F_1$ Pups:** For $F_1$ pups at 100 mg/kg/day, the survival index at day 4 and the weaning index at day 4 were reduced as compared to corresponding control values; however, the day 70 viability index for $F_1$ pups at 100 mg/kg/day was not different from the control. During the lactation period (days 0 to 21 postpartum), the number of $F_1$ pup deaths in the 100 mg/kg/day group was increased to 29 as compared to 4 for the control group. During lactation, all offspring of 3 $F_0$ dams at 100 mg/kg/day died (#4106, day 1; #4118, day 9; and #4122, day 13). Gross pathological examination of these three $F_0$ dams revealed nipple immaturity for #4106. Deaths of $F_1$ pups at 100 mg/kg/day appeared to be due to body undernourishment and no findings of milk curd in the stomach. Body weight gains for $F_1$ male pups from days 0 to 21 postpartum was reduced to 88.35%, 85.7, and 80.75% of the control, respectively. Body weight gains for $F_1$ female pups from days 0 to 21

postpartum were reduced to 87.3, 85.4, and 78.2% of the control, respectively. Body weight gains for $F_1$ male and female pups in omeprazole treatment groups from days 21 to 70 exceeded gains for corresponding control groups; although, body weights of $F_1$ pups on day 70 were depressed to 91.2% of corresponding control values. There were no treatment-related effects on physical, functional, or behavioral development.

Viability and body weights for $F_1$ fetuses from $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 10,32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| Viability of $F_1$ pups | | | | |
| Day 4 survival index, % | 98.7 (370/375) | 96.7 (324/325) | 98.2 (324/330) | 93.4 (313/335) |
| Day 21 weaning index, % | 99.5 (191/192) | 100 (178/178) | 98.9 (178/180) | 90.2 (165/183) |
| Day 70 viability Index, % | 100 (191/191) | 99.4 (177/178) | 99.4 (177/178) | 100 (165/165) |
| Body weight of $F_1$ pups, g (Male/Female) | | | | |
| Day 0 | 6.7/6.3 | 6.8/6.4 | 6.9/6.4 | 6.6/6.3 |
| Day 4 | 9.6/9.1 | 10.1/9.5 | 10.0/9.4 | 9.6/9.0 |
| Day 21 | 55.1/53.0 | 50.2/47.8 | 49.6/46.9 | 45.1/42.8 |
| Day 70 | 434.6/272.9 | 421.6/270.7 | 417.5/265.5 | 415.8/259.2 |

Gross pathological findings for $F_1$ pups that died during the lactation period (days 0 to 21 postpartum).

| Finding | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ pups examined | 4 | 10 | 5 | 29 |
| Body undernourishment | 0 | 0 | 1 (20%) | 2 (6.9%) |
| Stomach -no milk curd | 0 | 5 (50%) | 0 | 16 (55.2%) |

**Physical Development:** There were no treatment-related effects on physical development of $F_1$ pups with regard to pinna detachment, appearance of abdominal hair, opening of vagina, eruption of lower incisor, or descent of testis. The opening of the eyelid was delayed for $F_1$ pups at 32 and 100 mg/kg/day. On day 14 postpartum, opening of the eyelid in the 32 and 100 mg/kg/day groups was 43% (77/179) and 50% (83/166), respectively, as compared to 61.8% (118/191) for the control group. However, by day 17 postpartum, opening of the eyelid had occurred for all $F_1$ pups in the control and treatment groups.

**Functional Development:** There were no treatment-related effects on functional development of $F_1$ pups at day 21 postpartum (i.e., no effects on righting reflex, pupillary reflex, pain response, corneal reflex, pinna reflex, or Preyer's reflex).

**Behavioral Development:** There were no treatment-related effects on behavioral development (i.e., open field test at 5 weeks, water-filled multiple maze test at 7-8 weeks, and conditioned avoidance response at 9-10 weeks) of $F_1$ pups. In the open field test for $F_1$ female pups at 32 and 100 mg/kg/day, grooming activity in both of the two tests was reduced to 36-50% of the control; although, there was probably no biological significance to this change as no other parameters were altered. There were no gross pathological findings for $F_1$ pups used in behavioral tests.

**7. Fertility and Reproductive Performance of $F_1$ Rats:** Mating and fertility indexes for $F_1$ male and female rats in omeprazole treatment groups were unaffected as compared to the control group. Body weight gains of $F_1$ dams in omeprazole treatment groups from days 0 to 20 of gestation were unaffected as compared to the control group. For $F_1$ dams at cesarean section on day 20 of gestation, there were no treatment-related effects on corpora lutea/dam, implantations/dam, resorbed/dead fetuses, live fetuses/dam, placental weight, male to female ratio, and fetal body weight. Pre-implantation losses at 10, 32, and 100 mg/kg/day were increased to 8, 6, and 7.6%, respectively, as compared to 3.4% of the control; however, implantation sites/dam and live fetuses/dam were not decreased in a dose-related manner. There were no treatment-related gross pathological findings in $F_1$ male and female rats used in reproductive capacity tests. There were no treatment-related external malformations found in $F_2$ fetuses.

Mating and Fertility Indexes for $F_1$ rats derived from $F_0$ dams that received omeprazole by intravenous administration at doses of 0, 10, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| Days until mating | 3.5 | 3.1 | 2.8 | 2.5 |
| Mating Index, % | 95.8 (23/24) | 100 (23/23) | 100 (23/23) | 100 (21/21) |
| Fertility Index, % | 82.6 (19/23) | 95.7 (22/23) | 100 (23/23) | 95.2 (20/21) |

Cesarean section data for $F_1$ dams derived from $F_0$ dams that received omeprazole by intravenous administration at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 10 mg/kg/day | 32 mg/kg/day | 100 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ Dams | 19 | 21 | 22 | 20 |
| Corpora lutea/dam | 17.1 (325/19) | 16.7 (351/21) | 17.5 (385/22) | 16.4 (328/20) |
| Implantation sites/dam | 16.5 (314/19) | 15.4 (323/21) | 16.5 (362/22) | 15.2 (303/20) |
| Pre-implantation loss, % | 3.4 (11/325) | 8 (28/351) | 6 (23/385) | 7.6 (25/328) |
| Resorbed/dead fetuses<br>-Total<br>-Early<br>-Late | <br>23 (7.3%)<br>22<br>1 | <br>22 (6.8%)<br>22<br>0 | <br>21 (5.8%)<br>20<br>1 | <br>20 (6.6%)<br>19<br>1 |
| Live fetuses/dam | 15.3 (291/19) | 14.3 (301/21) | 15.5 (341/22) | 14.2 (283/20) |
| Male: Female Ratio | 1.06 (150/141) | 1.02 (152/149) | 1.29 (192/149) | 0.94 (137/146) |
| Fetal body weight, g<br>Male/Female | <br>3.64/3.40 | <br>3.58/3.43 | <br>3.70/3.48 | <br>3.78/3.58 |
| Placental weight, g | 0.52 | 0.54 | 0.57 | 0.51 |

In a Segment III perinatal and postnatal development study, pregnant $F_0$ female Sprague-Dawley rats received omeprazole by the intravenous route of administration at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum. Fetotoxicity was evident at doses of 10, 32 and 100 mg/kg/day; although, maternal toxicity was evident at the high dose. Postnatal development, as reflected by lower fetal body weight gains from days 0 to 21 postpartum, was impaired at all dose levels. The number of live pups/dam and live birth index (number of live $F_1$ births/number of implantations) was reduced at 10, 32, and 100 mg/kg/day. For $F_1$ pups at 100 mg/kg/day, the survival index at day 4 and the weaning index at day 21 were reduced as compared to corresponding control values; however, the day 70 viability index for $F_1$

pups at 100 mg/kg/day was not different from the control. Body weight gains for $F_1$ pups from days 0 to 21 postpartum in all treatment groups was impaired by >10%; however, body weight gains from days 21 to 70 were comparable to or exceeded those of corresponding control groups. There were no treatment-related effects on physical, functional, or behavioral development. No treatment-related effects on fertility and reproductive performance were evident for $F_1$ male and female rats. Maternal toxicity was evident at 100 mg/kg/day as transient decreases in spontaneous movement, tachypnea, and clonic convulsions were observed immediately after dosing in all animals throughout the administration period.

Segment III Study: Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Intravenous Route **(Report No. R-444).**

Testing Laboratory:

Date Started: May 25, 1992

Date Completed: November 19, 1992 (Translated from Japanese to English on June 15, 1998).

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies" and Yakuhatsu no. 870 (Pharmaceutical Affairs Bureau directive dated October 5, 1988), entitled "Amended regulations regarding pharmaceutical GLP and audits." A statement of compliance with the Quality Assurance Unit was included.

Animals: line female rats were used in the present study. On day 0 of gestation, female rats were approximately 11-weeks old and had a body weight range of 239-311 g.

Drug Batch: Omeprazole sodium, Lot No. J

Methods: In a Segment III perinatal and postnatal development study, female Sprague-Dawley rats received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 10 mg/kg/day from day 17 of gestation to day 21 postpartum in an attempt to identify a no effect dose with regard to $F_1$ pup body weight gain during days 0 to 21 postpartum. Doses were calculated from the weight of the omeprazole base. The control group was administered the vehicle,

ehicle or drug solution was administered into veins of the tail at a dose volume of 3 mL/kg. There were 24 pregnant $F_0$ female rats per group. Dose selection was based upon Report No. R-361 in which the high dose of 10 mg/kg/day was found to effect body weights of suckling $F_1$ pups. During the treatment period, animals were monitored for clinical signs of toxicity and moribundity/mortality three times per day, immediately prior to dosing, immediately after

dosing, and 1 hr after dosing. During other periods, animals were monitored once in the morning and once in the afternoon. Body weights of $F_0$ dams were measured on days 0, 4, 7, 11, and 14 of gestation, day 17 of gestation to delivery, and days 0, 2, 4, 7, 11, 14, 17, and 21 postpartum. Food consumption was measured on days 1, 4, 8, 11, 14, 17, and 20 of gestation and on days 2, 4, 7, 11, 14, 17, and 21 postpartum. Pregnant $F_0$ dams were allowed to deliver their offspring. The number of live births and stillbirths of $F_1$ offspring were counted on the day of delivery. Each $F_1$ offspring was examined for external malformations, sex was determined, and body weight was measured. $F_0$ dams that did not deliver by day 24 of gestation were sacrificed and submitted to gross pathological examination. The lactation status of $F_0$ dams was monitored for 21 days postpartum. $F_0$ dams were sacrificed on day 22 postpartum and submitted to gross pathological examination. The uteri were removed and the number of implantation scars were determined. Body weights of $F_1$ offspring were measured on days 0, 4, 7, 11, 14, 17, and 21 postpartum. On day 4, $F_1$ offspring were randomly culled to make 4 pups/sex/litter. $F_1$ offspring in excess of 8 were sacrificed, fixed, and preserved. Survival of F1 offspring was verified daily from days 0 to 21 postpartum. $F_1$ offspring were sacrificed on day 22 postpartum and submitted to gross pathological examination.

**Results:**

1. **Observed Effects:** None.

2. **Mortality:** None.

3. **Body Weight and Food Consumption:** There were no treatment-related effects on body weight gain or food consumption of $F_0$ dams from days 17 to 21 of gestation or days 0 to 21 postpartum. Body weights of control $F_0$ dams on days 17 and 21 of gestation were 387.3 and 428.8 g, respectively. Body weight gains of $F_0$ dams at 1, 3.2 and 10 mg/kg/day from days 17 to 20 of gestation were 102.6, 96.4, and 99.4% of the control, respectively. Body weights of $F_0$ dams on days 0 and 21 postpartum were 336.0 and 341.7 g, respectively. Body weight gains of $F_0$ dams at 1, 3.2, and 10 mg/kg/day from days 0 to 21 postpartum were 235.2, 216.3, and 236.7% of the control, respectively.

4. **Reproductive Data for $F_0$ Dams:** There were no treatment-related effects on gestation period, implantation sites/dam, live $F_1$ pups/dam, stillborn pup, live birth index, the male to female ratio, or the fetal body weight.

Delivery data for $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 10 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 1 mg/kg/day | 3.2 mg/kg/day | 10 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 24 | 23 | 24 |
| # $F_0$ dams that delivered liver pups | 24 | 24 | 23 | 24 |
| Gestation period (days) | 22.3 | 22.3 | 22.3 | 22.3 |
| Implantations/dam | 15.9 (381/24) | 15.6 (375/24) | 16.2 (372/23) | 16.5 (397/24) |
| Live $F_1$ pups/dam | 14.0 (335/24) | 14.1 (338/24) | 14.2 (326/23) | 14.7 (352/24) |
| Stillborn pups (%) | 15 (4.3%) | 10 (2.9%) | 15 (4.4%) | 9 (2.5%) |
| Unaccounted pups | 31 | 27 | 31 | 36 |
| Live Birth Index, % | 87.9 (335/381) | 90.1 (338/375) | 87.6 (326/372) | 88.7 (352/397) |
| Male/Female Ratio | 0.93 (161/174) | 0.91 (161/177) | 0.96 (160/166) | 0.89 (166/186) |
| Fetal body weight, g Male/Female | 6.8/6.4 | 6.8/6.4 | 6.7/6.4 | 6.8/6.4 |

5. Gross Pathological Examination of $F_0$ Dams: There were no treatment-related gross pathological findings for $F_0$ dams sacrificed on day 22 postpartum.

6. Viability and Development of $F_1$ Pups: There were no treatment-related effects on $F_1$ pup viability on days 4 or day 21. Body weight gains of $F_1$ male and female pups at 10 mg/kg/day from days 0 to 21 postpartum were slightly impaired (≤10%). Body weight gains of $F_1$ male pups at 1, 3.2, and 10 mg/kg/day from days 0 to 21 postpartum were 96.6, 95.6, and 90% of the control, respectively. Body weight gains of $F_1$ female pups at 1, 3.2, and 10 mg/kg/day from days 0 to 21 postpartum were 96.4, 95.1, and 90.1% of the control, respectively. There were no treatment-related gross pathological findings for $F_1$ pups sacrificed on day 22 postpartum.

Viability and body weights for $F_1$ fetuses from $F_0$ dams that received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 1 mg/kg/day | 3.2 mg/kg/day | 10 mg/kg/day |
|---|---|---|---|---|
| Viability of $F_1$ pups | | | | |
| Day 4 survival index, % | 97.6 (327/336) | 97.6 (330/338) | 99.1 (323/326) | 98.0 (344/351) |
| Day 21 weaning index, % | 100 (189/189) | 100 (191/191) | 99.4 (180/181) | 100 (188/188) |
| Body weight of $F_1$ pups, g (Male/Female) | | | | |
| Day 0 | 6.8/6.4 | 6.8/6.4 | 6.7/6.4 | 6.8/6.4 |
| Day 4 | 10.1/9.6 | 10.4/9.8 | 10.2/9.8 | 10.2/9.6 |
| Day 21 | 56.7/53.7 | 55/52.0 | 53.7/51.4 | 51.7/49 |

In a Segment III perinatal and postnatal development study, female Sprague-Dawley rats received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 10 mg/kg/day from day 17 of gestation to day 21 postpartum. Postnatal development, as reflected by slightly lower body weight gains, was impaired at 10 mg/kg/day. Body weight gains of $F_1$ male and female pups at 10 mg/kg/day from days 0 to 21 postpartum were slightly impaired (≤10%). There was no evidence of maternal toxicity at any dose.

Segment III Perinatal and Postnatal Development Study in Rats that Received Omeprazole by the Oral Route of Administration (Report No. R-143).

Testing Laboratory:

Date Started: January 20, 1987

Date Completed: January 20, 1988 (Translation from Japanese to English, June 12, 1998).

GLP Compliance: This study was conducted in accordance with the Ministry of Health and Welfare Yakuhatsu no. 313 (Pharmaceutical Affairs Bureau directive dated March 31, 1982), entitled "Standards for the performance of pharmaceutical safety studies." A statement of compliance with the Quality Assurance Unit was included.

Animals: Pregnant line rats were used. Pregnant $F_0$ female rats were approximately 11-weeks old and had a body weight range of 218-260 g.

Drug Batch: Omeprazole, Lot number 124

Methods: In a Segment III perinatal and postnatal development study, $F_0$ dams received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum. Control animals received the vehicle,

The dose volume was 5 mL/kg. There were 24 $F_0$ female rats per group that were confirmed to have mated. During the treatment period, animals were monitored for clinical signs of toxicity and moribundity/mortality three times per day, immediately prior to dosing, immediately after dosing, and 1 hr after dosing. During other periods of the study, animals were monitored twice per day, once in the morning and once in the afternoon. $F_0$ dams were weighed on days 0, 3, 7, 11, and 14 of gestation, day 17 of gestation to delivery, and days 0, 2, 4, 7, 11, 14, 17, and 21 of lactation. Food consumption was measured on days 1, 4, 8, 11, 14, 17, and 20 of gestation, and on days 2, 4, 7, 11, 14, 17, and 21 of lactation. Pregnant $F_0$ female rats were allowed to deliver naturally and the delivery data, gestational period, and birth index were determined. The suckling status of $F_1$ offspring were monitored for 21 days after birth. $F_0$ dams were sacrificed on day 22 postpartum and submitted to gross pathological examination. The uteri were removed and the number of implantation scars were counted. $F_0$ dams that did not deliver by day 24 of gestation were sacrificed, the content of uteri were examined, and data on animals determined to be infertile were excluded. For $F_1$ offspring, the number of live births and stillbirths were counted on the day of delivery. Stillbirths were submitted to gross pathological examination and preserved. Each live $F_1$ birth was examined for external malformations, the sex was determined, and body weight was measured. The $F_1$ offspring were weighed twice a week until day 21 of lactation and one a week from days

21 to 70. On day 4 postpartum, the $F_1$ offspring were randomly culled to make 4 rats/ sex/litter, when possible. For $F_1$ pups, viability, development (i.e., physical, functional, and behavioral), and fertility and performance were assessed as described earlier in methods for Report No. R-249.

**Results:**

1. **Observed Effects with $F_0$ Dams:** Decreased spontaneous movement was observed on day 22 of gestation and day 0 postpartum for a $F_0$ dam (#4104), whose $F_1$ offspring were all found to be stillborn. For 8 $F_0$ dams at 320 mg/kg/day, salivation was observed, transiently or sporadically (i.e., 1-3 animals/day), immediately after dosing between days 7 and 21 postpartum.

2. **Mortality of $F_0$ Dams:** None.

3. **Body Weight and Food Consumption of $F_0$ Dams:** Between days 17 and 20 of gestation, body weight gain and food consumption were suppressed for $F_0$ dams at 320 mg/kg/day. Body weights of control $F_0$ dams on days 17 and 20 of gestation were 353.2 and 393.4 g, respectively. Body weight gains of $F_0$ dams at 3.2, 32, and 320 mg/kg/day between days 17 and 20 of gestation were 103.6, 93.7, and 67.1% of the control, respectively. Food consumption for $F_0$ dams at 320 mg/kg/day on day 20 of gestation was decreased to 82.1% of the control (23.5 g/rat/day). Body weights for $F_0$ dams on days 0 and 21 postpartum were 303.8 and 319.7 g, respectively. Body weight gains for $F_0$ dams at 3.2, 32, and 320 mg/kg/day between days 0 and 21 postpartum were 119.3, 100.1 and 186.6% of the control, respectively.

4. **Reproductive Data for $F_0$ Dams:** The number of stillborn $F_1$ pups at 320 mg/kg/day was increased to 6.7% as compared to 2% for the control. Based upon numbers of implantation sites, live pups, and stillborn pups, the sponsor did not account for 10, 13, 19, and 21 pups at doses of 0, 3.2, 32, and 320 mg/kg/day, respectively. The live birth index (i.e., number of live born/number of implantations) at 320 mg/kg/day was decreased to 88.2% as compared to 95.3% for the control.

Delivery data for $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # Pregnant $F_0$ dams | 24 | 23 | 24 | 24 |
| # $F_0$ dams that delivered liver pups | 24 | 23 | 24 | 23 |
| Gestation period (days) | 21.8 | 21.9 | 21.9 | 22.0 |
| Implantations/dam | 15.2 (364/24) | 15.7 (361/23) | 15.6 (374/24) | 15.9 (381 24) |
| Live $F_1$ pups/dam | 14.5 (347/24) | 14.9 (342/23) | 14.3 (344/24) | 14.0 (336 24) |
| Stillborn pups (%) | 7 (2.0%) | 6 (1.7%) | 11 (3.1%) | 24 (6.7%) |
| Unaccounted pups | 10 | 13 | 19 | 21 |
| Male/Female Ratio | 0.94 (168/179) | 1.06 (176/166) | 0.94 (167/177) | 1.05 (172 164) |
| Live Birth Index | 95.3 | 94.7 | 92.0 | 88.2 |

**5. Gross Pathological Examination of $F_0$ Dams:** One control $F_0$ dam (1116) was necropsied on day 4 postpartum due to death of all pups and found with nipple and mammary gland immaturity. One $F_0$ dam (4104) at 320 mg/kg/day was necropsied on day 0 postpartum due to stillbirth of all pups and found with nipple and mammary gland immaturity. One $F_0$ dam (4121) at 320 mg/kg/day was necropsied on day 1 postpartum due to death of all pups and found with nipple immaturity. Nipple and mammary gland immaturity of $F_0$ dams do appear to have any relationship to omeprazole treatment.

**6. Viability and Development of $F_1$ Pups:** There were no treatment-related effects on $F_1$ pup viability on days 4, 21, and 70. Body weight gains of $F_1$ male rats at 32 and 320 mg/kg/day from days 0 to 21 postpartum were decreased to 84.8 and 78.3% of the control, respectively. Body weight gains of $F_1$ female rats at 32 and 320 mg/kg/day from days 0 to 21 postpartum were decreased to 86.0 and 84.8% of the control, respectively. Body weight gains of $F_1$ male and female rats in omeprazole treatment groups from days 21 to 70 postpartum were comparable to or greater than corresponding control groups. There were no gross pathological findings in $F_1$ pups culled on day 4 postpartum. A $F_1$ male pup (4101-02) at 320 mg/kg/day died on day 50 postpartum. Gross pathological findings for this animal were as follows: submandibular gland and lymph node, dark red change; lung, dark red spots; heart, spleen, pancreas, and liver, pale in color; and stomach and intestine, retention of gas. There was a dose-related increased incidence of red spots or disseminated red spots in the lungs of $F_1$ offspring in omeprazole treatment groups.

Viability and body weights for $F_1$ fetuses from $F_0$ dams that received omeprazole by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| Viability of $F_1$ pups | | | | |
| Day 4 survival index, % | 96.8 (336/347) | 99.1 (338/341) | 98.8 (340/344) | 94.0 (314/334) |
| Day 21 weaning index, % | 92.9 (171/184) | 96.2 (177/184) | 97.4 (186/191) | 94.9 (167/176) |
| Day 70 viability Index, % | 100 (171/171) | 99.4 (176/177) | 98.4 (183/186) | 98.2 (164/167) |
| Body weight of $F_1$ pups, g (Male/Female) | | | | |
| Day 0 | 6.0/5.9 | 6.3/5.9 | 6.5/6.0 | 5.9/5.6 |
| Day 4 | 8.6/8.2 | 8.9/8.5 | 9.3/8.7 | 8.1/7.7 |
| Day 21 | 46.4/44.9 | 48.0/46.8 | 43.6/40.8* | 37.0*/37.6* |
| Day 70 | 393.2/239.0 | 398.1/244.5 | 383.9/240.0 | 376.7*/238.1 |

$p \leq 0.05$

**Physical Development:** There were no treatment-related effects on physical development of $F_1$ pups (i.e., no effect on pinna detachment, appearance of abdominal hair, opening of vagina, eruption of lower incisor, opening of eyelid, or descent of testis).

**Functional Development:** There were no treatment-related effects on functional development of $F_1$ pups at day 21 postpartum (i.e., no effects on righting reflex, pupillary reflex, pain response, corneal reflex, pinna reflex, or Preyer's reflex).

**Behavioral Development:** There were no treatment-related effects on behavioral development of $F_1$ pups. $F_1$ pups used in behavioral tests were sacrificed at 10 weeks. Findings for 1 male (4.3%) at 32 mg/kg/day included red spots in the lung. Findings for 1 female (4.3%) at 320 mg/kg/day included disseminated dark red spots and red spots.

Gross pathological findings for $F_1$ pups at 0, 3.2, 32, and 320 mg/kg/day on day 70 postpartum.

| Organ | 0 mg/kg/day | | 3.2 mg/kg/day | | 32 mg/kg/day | | 320 mg/kg/day | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| n = | 39 | 41 | 45 | 40 | 48 | 41 | 43 | 37 |
| **Lungs** | | | | | | | | |
| -red spots or dark red spots | 1 (2.6%) | 0 | 1 (2.2%) | 0 | 1 (2.1%) | 1 (2.4%) | 3 (7.0%) | 1 (2.7%) |
| -disseminated dark red spots | 0 | 0 | 0 | 0 | 1 (2.1%) | 1 (2.4%) | 0 | 0 |
| **Uterus** | | | | | | | | |
| -luminal dilatation and retention of fluid | - | 0 | - | 3 (7.5%) | - | 1 (2.4%) | - | 2 (5.4%) |

**7. Fertility and Reproductive Performance of $F_1$ Rats:** Body weight gains and food consumption were unaffected in $F_1$ dams from omeprazole treatment groups during gestation. Mating and fertility indexes for $F_1$ rat at 320 mg/kg/day were lower than the control after the 1st mating, but comparable to the control after the 2nd mating. Further, corpora lutea/dam, implantation sites/dam, pre-implantation loss, resorbed/dead fetuses, live $F_2$ fetuses/dam, the male to female ratio, fetal body weight, and placental weight were unaffected by omeprazole treatment. There were no treatment-related external malformations found in $F_2$ fetuses. There were no treatment-related gross pathological findings in $F_1$ male and female rats used in the reproductive capacity test.

Mating and Fertility Indexes for $F_1$ rats derived from $F_0$ dams that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Mating | Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|---|
| 1st | Days until mating | 3.3 | 3.1 | 2.3 | 3.3 |
| | Mating Index, % | 100 (23/23) | 91.3 (21/23) | 95.8 (23/24) | 81.0* (17/21) |
| | Fertility Index, % | 91.3 (21/23) | 95.2 (20/21) | 95.7 (22/23) | 82.4 (14/17) |
| 1st + 2nd | Mating Index, % | 100 (23/23) | 95.7 (22/23) | 100 (24/24) | 90.5 (19/21) |
| | Fertility Index, % | 91.3 (21/23) | 95.5 (21/22) | 95.8 (23/24) | 84.2 (16/19) |

$p \leq 0.05$

Cesarean section data for $F_1$ dams derived from $F_0$ dams that received omeprazole by oral gavage at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum.

| Parameter | 0 mg/kg/day | 3.2 mg/kg/day | 32 mg/kg/day | 320 mg/kg/day |
|---|---|---|---|---|
| # $F_1$ Dams | 21 | 21 | 22 | 15 |
| Corpora lutea/dam | 16.0 (337/21) | 17.0 (356/21) | 15.4 (339/21) | 16.9 (253/15) |
| Implantation sites/dam | 14.5 (305/21) | 16.0 (336/21) | 14.3 (315/22) | 15.8 (237/15) |
| Pre-implantation loss, % | 9.5 (32/337) | 5.6 (20/356) | 7.1 (24/339) | 6.3 (16/253) |
| Resorbed/dead fetuses<br>-Total<br>-Early<br>-Late | <br>23 (7.5%)<br>21<br>2 | <br>14 (4.2%)<br>14<br>0 | <br>21 (6.7%)<br>21<br>0 | <br>12 (5.1%)<br>12<br>0 |
| Live fetuses/dam | 13.4 (282/21) | 15.3 (322/21) | 13.4 (294/22) | 15.0 (225/15) |
| Male: Female Ratio | 0.88 (132/150) | 0.75 (138/184) | 0.86 (136/158) | 0.94 (109/116) |
| Fetal body weight, g<br>Male/Female | <br>3.61/3.44 | <br>3.56/3.36 | <br>3.72/3.55 | <br>3.62/3.41 |
| Placental weight | 0.47 | 0.48 | 0.51 | 0.48 |

In a Segment III perinatal and postnatal development study, $F_0$ dams received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum. Toxic effects on postnatal development, as reflected by decreased body weight from days 0 to 21 postpartum, were evident at doses of 32 and 320 mg/kg/day. There was no evidence of maternal toxicity during days 0 to 21 postpartum. The number of stillborn $F_1$ pups at 320 mg/kg/day was increased to 6.7% as compared to 2% for the control. The live birth index (i.e., number of live born/number of implantations) at 320 mg/kg/day was decreased to 88.2% as compared to 95.3% for the control. Body weight gains for $F_1$ rats at 32 and 320 mg/kg/day from days 0 to 21 postpartum were impaired by >10%; however, body weight gains of $F_1$ rats in omeprazole treatment groups from days 21 to 70 postpartum were comparable to or greater than corresponding control groups. There were no treatment-related effects on physical, functional, or behavioral development of $F_1$ pups. The reproductive capacity of $F_1$ rats was unaffected by omeprazole treatment. There was some evidence of $F_0$ maternal toxicity at 320 mg/kg/day from days 17 to 20 of gestation, as body weight gain and food consumption were suppressed; however, body weight gain from days 0 to 21 postpartum was greater than that observed for controls.

## PROPOSED TEXT OF CHANGES IN THE LABELING FOR OMEPRAZOLE.

The label is according to 21 CFR 201.50, Subpart B (April 1, 1998). However, the following changes should be incorporated:

### 1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

### Current Approved Version:

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of

this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an in vitro Ames Salmonella typhimurium assay, an in vitro mouse lymphoma cell assay and an in vivo rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an in vivo bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

**Sponsor's New Version:**

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (0.7 to times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. [illegible] No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

Omeprazole at oral doses up to
body surface area) was found to have no effect on fertility and reproductive performance

**Evaluation:** The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998). There were some errors in calculating dosages in rat carcinogenicity studies relative to the human recommended dosage based on body surface area. The sponsor has provided no rationale for replacement of the Segment I fertility and reproductive performance study in rats conducted by AB Astra Toxicology Laboratories with the study conducted

**Proposed Version:**

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day

ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about times the human dose ) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group.

No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

Omeprazole at oral doses up to 138 mg/kg/day in rats [redacted] the [redacted] body surface [redacted] was found to have no effect on fertility and reproductive performance.

**2. Pregnancy:**

**Current Approved Version:**

Pregnancy Category C
Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clarithromycin
Pregnancy Category C. See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

**Sponsor's New Version:**

Omeprazole
Pregnancy Category B

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy

Clarithromycin

Pregnancy Category C. See WARNINGS (above) and full prescribing information for clarithromycin before using in pregnant women.

**Evaluation:** The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998). The sponsor has provided no rationale for replacement of Segment II teratology studies in rats and rabbits conducted by AB Astra Toxicology Laboratories with studies conducted Segment III perinatal and postnatal development studies in rats conducted by appear to confirm Segment III studies conducted by AB Astra Toxicology Laboratories. Human studies and studies involving the combination of omeprazole and clarithromycin were not evaluated in this review.

**Proposed Version:**

Pregnancy Category C

3. Nursing Mothers:

Current Approved Version:

It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Sponsor's New Version:

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 ml of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Evaluation: The proposed new text appears to be in accordance with 21CFR, 201.50, Subpart B (April 1, 1998); although, human studies were not evaluated in this review.

**Sponsor's New Version:**

No changes.

## SUMMARY AND EVALUATION

Omeprazole (Prilosec™) is an approved drug product classified as an inhibitor of gastric parietal cell $H^+,K^+$-ATPase. In the present supplement, the sponsor has submitted additional reproductive toxicology studies conducted in rats and rabbits with the intention of providing support for a change in the Pregnancy Category Label from C

Studies reviewed under NDA 19,810 in 1989 were conducted by AB Astra Toxicology Laboratories in compliance with GLP regulations issued on December 22, 1978 by the United States FDA. However, additional new studies in the present supplement were conducted at Japan with no indications of compliance with United States FDA GLP regulations at the times that studies were performed. Further, the source of drug varied between studies reviewed in 1989 and additional new studies submitted in the present supplement, which introduces an unknown variable in the analysis of these studies. The source of drug for studies reviewed in 1989 was AB Hassle of Sweden, while the sources of drug for additional new studies in the present supplement were The final reports of these additional new studies were issued between 1987 and 1992. Translation from Japanese to English apparently occurred in 1998. Studies originally submitted under NDA 19,810 dated June 30, 1988 and resubmitted in the present supplement were as follows: Segment I fertility and reproductive performance study in rats using oral administration; Segment II teratology study in rats using oral administration; Segment II teratology study in rabbits using oral administration; Segment III perinatal and postnatal development study in rats using oral administration; and Segment III study: extended perinatal and postnatal study in rats after oral administration of omeprazole during late pregnancy and lactation. New studies included in the present supplement were as follows: whole body autoradiographic study on the distribution of $^{14}C$-omeprazole in mice after intravenous or oral administration (not relevant); Distribution, metabolism, and excretion in rats after intravenous administration; Placental transfer of omeprazole in maternal and fetal sheep published in Developmental Pharmacology and Therapeutics 9: 323-331, 1986 (not relevant); Segment I fertility and reproductive performance study in rats using intravenous administration; Segment I fertility and reproductive performance study in rats using oral administration; Segment II teratology study in rats using intravenous administration; Segment II teratology study in rats using oral administration; Segment II teratology study in rabbits using intravenous administration; Segment III perinatal and postnatal development study in rats using intravenous administration; Segment III perinatal and postnatal development study in rats using intravenous administration; and Segment III perinatal and postnatal development study in rats using oral administration.

The distribution of omeprazole was examined in pregnant and lactating female rats following intravenous administration. For pregnant female rats, 0.43% of the administered dose was found in the fetus (whole body). In lactating female rats, evidence of omeprazole-related radioactivity was found in the milk.

In a Segment I study reviewed in NDA 19,810 dated May 25, 1989, the effects of omeprazole administered by the oral route at doses of 0, 13.8, 43.1, and 138 mg/kg/day were assessed on fertility and reproductive performance in male and female Sprague-Dawley rats. Male rats were treated for 9 weeks prior to mating and during the mating period. Female rats were treated for 2 weeks prior to mating, through the mating period, and up to day 21 of gestation or day 21 postpartum. Fertility and reproductive performance were apparently unaffected at oral doses ≤138 mg/kg/day in rats; although, the sponsor did not provide any data on the breeding performance of male rats. There was evidence for fetotoxicity and developmental toxicity with $F_1$ pups from all treatment groups. There was no evidence of maternal toxicity at any dose. No fetal examinations for teratogenic effects were conducted even though the dams were sacrificed on day 21. For dams sacrificed on day 21 of gestation, there was a dose-related increase in post-implantation losses in all treatment groups as compared to the control. Consequently, there was a dose-related decrease in the number of viable fetuses/dam in all treatment groups as compared to the control. For dams allowed to deliver their offspring, there were dose-related decreases in the number of viable pups born/dam and birth weight in all treatment groups as compared to the control. Survival of pups was adversely affected up to day 21 postpartum in a dose-related manner in all treatment groups as compared to the control. Body weight gain in pups from all treatment groups was retarded at days 7 and 21 postpartum.

In a Segment I study submitted in the present supplement, the effects of omeprazole administered by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day were assessed on fertility and reproductive performance in male and female Sprague-Dawley rats. Male rats were treated for 9 weeks prior to mating, during the mating period, and up to the day before sacrifice. Female rats were treated for 2 weeks prior to mating, during the mating period, and to day 7 of gestation. Omeprazole at intravenous doses ≤100 mg/kg/day had no effect on fertility and reproductive performance in rats. Implantation sites/dam at 100 mg/kg/day were decreased to 12.4 as compared to 14.7 for the control. Pre-implantation loss at 100 mg/kg/day was increased to 21.6% as compared to 10.2% for the control. Live fetuses/dam at 100 mg/kg/day were decreased to 11.2 as compared to 13.7 for the control. No listings were provided for individual animals.

In a Segment I study submitted in the present supplement, the effects of omeprazole administered by the oral route at doses of 0, 3.2, 32, and 320 mg/kg/day were assessed on fertility and reproductive performance in male and female Sprague-Dawley rats. Male rats were treated with vehicle or omeprazole for 9 weeks prior to mating, during the mating period, and until the day prior to sacrifice. Female rats were treated with vehicle or omeprazole for 2 weeks prior to mating, during the mating period, and until day 7 of gestation. Omeprazole at doses ≤320 mg/kg/day had no effects on fertility or reproductive performance in rats. Body weight gain was impaired by >10% for male rats at 320 mg/kg/day. Body weight gains were impaired by >10% for female rats at 320 mg/kg/day during the pre-mating period and for female rats at 32 and 320 mg/kg/day from days 0 to 7 of gestation. There were no treatment-related effects on

number of live fetuses/dam. Fetal examinations revealed no treatment-related external, visceral, or skeletal malformation or variations; however, it should be noted that drug was not administered during the period of organogenesis. The final report of this study was issued on January 20, 1988 and could have conceivably been submitted to NDA 19,810 dated June 30, 1988; however, it was not submitted to the Division until October 7, 1998.

In a Segment II teratology study reviewed under NDA 19,810 dated May 25, 1989, pregnant female Sprague-Dawley rats received omeprazole by the oral route at doses of 0, 13.8, 43.2, and 138 mg/kg/day from days 6 to 15 of gestation. Omeprazole at oral doses ≤ 138 mg/kg/day was not teratogenic in rats. Omeprazole at oral doses ≤138 mg/kg/day produced no signs of any maternal toxicity, embryotoxicity, teratogenicity or fetotoxicity.

In a Segment II teratology study submitted in the present supplement, pregnant female Sprague-Dawley rats received omeprazole by the intravenous route at doses of 0, 10, 32, and 100 mg/kg/day from days 7 to 17 of gestation. Omeprazole at intravenous doses ≤ 100 mg/kg/day was not teratogenic in rats. For $F_0$ dams allowed to deliver their offspring, the sponsor did not account for all $F_1$ pups based upon numbers of implantation sites and live births.

In a Segment II teratology study submitted in the present supplement, pregnant female Sprague-Dawley rats received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from days 7 to 17 of gestation. There were 36 pregnant female rats/group: 24/group for cesarean section on day 20 and 12/group for natural delivery. Omeprazole at oral doses ≤320 mg/kg/day produced no structural teratogenic effects; however, toxic effects with regard to behavioral development were evident. For behavioral development of $F_1$ pups, treatment-related changes were observed in the open field test and conditioned avoidance response, but not in the water-filled multiple maze test. In open field tests with $F_1$ male rats, ambulation was increased for all treatment groups. Defecation and urination were increased for $F_1$ male rats at 32 and 320 mg/kg/day. In open field tests with $F_1$ female rats, ambulation, rearing, and grooming were increased at 32 and 320 mg/kg/day. Latency was decreased in all $F_1$ female treatment groups. For the conditioned avoidance response, low avoidance index values and prolonged latency were observed for $F_1$ male rats at 32 and 320 mg/kg/day; although, no changes were observed for $F_1$ female rats. No listings were provided for individual animals. The sponsor did not account for the pregnancy status in all $F_0$ female rats. For $F_0$ dams allowed to deliver their offspring, the sponsor did not account for all $F_1$ pups based upon numbers of implantation sites and live births.

In a Segment II teratology study reviewed under NDA 19,810 dated May 25, 1999, pregnant female rabbits received omeprazole by the oral route of administration at doses of 0, 6.9, 27.6, 69.1, and 138.2 mg/kg/day from days 6 to 18 of gestation. Treatment at 138.2 mg/kg/day had to be discontinued from day 14 due to severe signs of clinical toxicity (i.e., anorexia and reduced water intake). Omeprazole at doses ≤69.1 mg/kg/day was not teratogenic in female rabbits. Omeprazole at maternally

nontoxic doses ≤69.1 mg/kg/day was disruptive to pregnancy. Further, omeprazole treatment at doses ≤69.1 mg/kg/day was embryotoxic and fetotoxic as it produced dose-related increases in embryonic deaths/dam and in percent fetal losses and a dose-related decrease in the number of viable fetuses/dam.

In a Segment II teratology study submitted in the present supplement, pregnant female rabbits received omeprazole by the intravenous route at doses of 0, 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation. Omeprazole at intravenous doses ≤32 mg/kg/day was not teratogenic in rabbits. Fusion of the sternebrae, a skeletal malformation, was observed for 1 fetus (1.6%) at 10 mg/kg/day and 1 fetus (2.1%) at 32 mg/kg/day; although, these findings appear to fall within the background incidence. Spontaneous abortions occurred for 1 animal at 10 mg/kg/day on day 20 of gestation and 1 animal at 32 mg/kg/day on day 27 of gestation. The sponsor attributed decreased food consumption as the probable cause of abortions in these 2 animals; although, food consumption was decreased by >15% in all omeprazole-treatment groups. The pre-implantation loss at 32 mg/kg/day was increased to 23.1% as compared to 15.1% for the control. Consequently, live fetuses/dam at 32 mg/kg/day were decreased to 7.5 as compared to 8.9 for the control. Implantation sites/dam at 32 mg/kg/day were decreased to 7.7 as compared to 9.0 for controls. Pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation lost 0.5, 1.9, and 4.6% of body weight on day 6, respectively. Food consumption for pregnant female rabbits that received omeprazole at intravenous doses of 3.2, 10, and 32 mg/kg/day from days 6 to 18 of gestation was decreased to 82.6, 73.5, and 58.1% of the control (143.4 g/rabbit/day), respectively.

In a Segment III perinatal and postnatal development study reviewed under NDA 19,810 dated May 25, 1989, omeprazole was administered by the oral route at doses of 0, 13.8, 43.1, or 138 mg/kg/day to female $F_0$ Sprague-Dawley rats from day 15 of gestation to day 20 postpartum. Omeprazole produced a dose-related developmental toxicity for $F_1$ pups in all treatment groups as evidenced by decreased body weights on day 21 postpartum.

In a Segment III study reviewed under NDA 19,810 dated May 25, 1989, decreased mean pup body weights observed on day 21 postpartum following oral treatment of dams with omeprazole during late gestation and the lactation period were further investigated. Groups of female rats received omeprazole and/or vehicle by the oral route from day 15 of gestation to day 20 postpartum. Group 1 received the vehicle from day 15 of gestation to day 20 postpartum. Group 2 received omeprazole at 138 mg/kg/day from day 15 of gestation to day 10 postpartum and vehicle from days 11 to 20 postpartum. Group 3 received vehicle from day 15 of gestation to day 10 postpartum and omeprazole at 138 mg/kg/day from days 11 to 20 postpartum. Group 4 received omeprazole from day 15 of gestation to day 20 postpartum. Treatment of dams in Group 4 with omeprazole produced developmental toxicity in their pups as evidenced by a 12.4% retardation in body weight gain when compared to controls on day 21 postpartum.

In a Segment III perinatal and postnatal development study submitted in the present supplement, pregnant $F_0$ female Sprague-Dawley rats received omeprazole by the intravenous route of administration at doses of 0, 10, 32, and 100 mg/kg/day from day 17 of gestation to day 21 postpartum. Fetotoxicity was evident at doses of 10, 32 and 100 mg/kg/day; although, maternal toxicity was evident at the high dose. Postnatal development, as reflected by lower fetal body weight gains, was impaired at all dose levels. The number of live pups/dam and live birth index (number of live $F_1$ births/number of implantations) was reduced at 10, 32, and 100 mg/kg/day. For $F_1$ pups at 100 mg/kg/day, the survival index at day 4 and the weaning index at day 21 were reduced as compared to corresponding control values; however, the day 70 viability index for $F_1$ pups at 100 mg/kg/day was not different from the control. Body weight gains for $F_1$ pups from days 0 to 21 in all treatment groups was impaired by >10%; however, body weight gains from days 21 to 70 postpartum, with no drug exposure, were comparable to or exceeded those of corresponding control groups. There were no treatment-related effects on physical, functional, or behavioral development. No treatment-related effects on fertility and reproductive performance were evident for $F_1$ male and female rats. Maternal toxicity was evident at 100 mg/kg/day as transient decreases in spontaneous movement, tachypnea, and clonic convulsions were observed immediately after dosing in all animals throughout the administration period.

In a Segment III perinatal and postnatal development study submitted in the present supplement, female Sprague-Dawley rats received omeprazole by the intravenous route at doses of 0, 1, 3.2, and 10 mg/kg/day from day 17 of gestation to day 21 postpartum in an attempt to identify a no effect dose with regard to $F_1$ pup body weight gain during days 0 to 21 postpartum. Postnatal development, as reflected by slightly lower body weight gains, was impaired at 10 mg/kg/day. Body weight gains of $F_1$ male and female pups at 10 mg/kg/day from days 0 to 21 postpartum were slightly impaired (≤10%). There was no evidence of maternal toxicity at any dose.

In a Segment III perinatal and postnatal development study submitted in the present supplement, $F_0$ dams received omeprazole by the oral route of administration at doses of 0, 3.2, 32, and 320 mg/kg/day from day 17 of gestation to day 21 postpartum. Toxic effects on postnatal development, as reflected by decreased pup body weight from days 0 to 21 postpartum, were evident at doses of 32 and 320 mg/kg/day. There was no evidence of maternal toxicity during days 0 to 21 postpartum. The number of stillborn $F_1$ pups at 320 mg/kg/day was increased to 6.7% as compared to 2% for the control. The live birth index (i.e., number of live born/number of implantations) at 320 mg/kg/day was decreased to 88.2% as compared to 95.3% for the control. Body weight gains for $F_1$ rats at 32 and 320 mg/kg/day from days 0 to 21 postpartum were impaired by >10%; however, body weight gains of $F_1$ rats in omeprazole treatment groups from days 21 to 70 postpartum, with no drug exposure, were comparable to or greater than corresponding control groups. There were no treatment-related effects on physical, functional, or behavioral development of $F_1$ pups. The reproductive capacity of $F_1$ rats was unaffected by omeprazole treatment.

In the present supplement, the sponsor has submitted additional reproductive toxicology studies conducted in rats and rabbits with the intention of providing support for a change in the Pregnancy Category Label from C to B. Reproductive toxicology studies with omeprazole conducted by AB Astra Toxicology and reviewed under NDA 19,810 dated May 25, 1989 provided evidence of toxic effects that placed this drug under Pregnancy Category C. In a Segment II teratology study with rabbits, omeprazole in an oral dose range of 6.9 to 69.1 mg/kg/day produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In a Segment III perinatal and postnatal development study in rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at oral doses of 13.8 to 138.0 mg/kg/day. In the present supplement, additional reproductive toxicology studies have been provided , Japan. It was not apparent if these studies were conducted in compliance with GLP regulations issued by the FDA. Further, the source of drug varied between studies reviewed in 1989 and new studies submitted in the present supplement, which introduces an unknown variable in the analysis of these studies. Most significantly, these additional reproductive toxicology studies with omeprazole in the present supplement reveal evidence of adverse effects not observed in earlier studies as well as confirming previously observed toxic effects. In a Segment II teratology study with rats, omeprazole at oral doses ≤ 320 mg/kg/day produced no structural teratogenic effects; however, toxic effects with regard to behavioral development were evident, which had not been described in earlier studies. Three Segment III perinatal and postnatal development studies conducted in rats using oral and intravenous routes of administration confirmed earlier observations of postnatal developmental toxicity in offspring resulting from parents treated with omeprazole. These additional studies in the present supplement do not change the conclusions of reviews in 1989 of reproductive toxicology studies with omeprazole submitted under NDA 19,810. From a preclinical standpoint, omeprazole should remain under Pregnancy Category C.

It should be noted that the sponsor also submitted data from three clinical epidemiological studies, which were considered inadequate in the Medical Officer's Review (Document Room Date of January 22, 1999) to support a change in Pregnancy Category labeling. To support a change in Pregnancy Category C classification to Pregnancy Category B, the Medical Officer's Review recommended that the sponsor plan a prospective, controlled study of omeprazole in women having a serious medical need for the drug during pregnancy.

The label is not according to 21 CFR, 201.50 Subpart B (April 1, 1998), and changes in text as outlined in the review portion are needed.

**RECOMMENDATION:**

From a preclinical standpoint, omeprazole should remain under Pregnancy Category C. The label is not according to 21 CFR, 201.50 Subpart B (April 1, 1998), and changes in text as outlined in the review portion are needed. The information listed below should be communicated to the sponsor.

1. Were the reproductive toxicology studies conducted by of Japan performed in compliance with United States FDA Good Laboratory Practice Guidelines? If different regulatory guidelines were used for conduct of these studies, how do they differ from United States FDA Good Laboratory Practice Guidelines?

2. For Report No. R-120, the sponsor should account for the pregnancy status of all $F_0$ dams (i.e., pregnant, not pregnant, infertile).

3. For Report numbers R-120, R-249, R-361, R-444, and R-143 in which dams were allowed to deliver their offspring, based upon the numbers of implantations, live born fetuses, and stillborn fetuses, there appeared to be missing fetuses. The sponsor should attempt to account for all fetuses in these reports.

4. Line listings for individual dams were not provided were Report numbers R-241, R-142, or R-120.

Timothy W. Robison 8-11-99
Timothy W. Robison, Ph.D. Date

cc:
Orig NDA 19,810
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison

1. Concur.
2. A Team Leader Memorandum will

R/D Init.: J. Choudary 7/23/99

TWR/hw/8/5/99 & 8/11/99
C:\MSWORD\PHARM\N\19810908.0TR

8/11/99

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# NDA 19-810/S-003 & S-058

# ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

## 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 (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.

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

| | | |
|---|---|---|
| 1. | Applicant | Astra Merck Inc. |
| 2. | Patent No.<br>Expiration Date | 4,786,505<br>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. 4,853,230 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 (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.

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

| | | |
|---|---|---|
| 1. | Applicant | Astra Merck Inc. |
| 2. | Patent No.<br>Expiration Date | 4,853,230<br>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.

## 1.0 PATENT INFORMATION

Patent information for omeprazole (PRILOSEC®) is attached. Information and declarations for the following patent numbers are included:

Patent Nos. 4,786,505

4,853,230

4,255,431

4,636,499

5,093,342

5,599,794

5,629,305

All patent information included in this supplement has been previously submitted to the Food and Drug Administration.

Attachment B

ASTRA MERCK

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

| | |
|---|---|
| 1. Applicant | Astra Merck Inc. |
| 2. Patent No.<br>Expiration Date | 4,255,431<br>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 section 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. |

Attachment B

ASTRA MERCK

## 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 and 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
Executive Director,
Regulatory Affairs
Astra Merck Inc.

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

| | |
|---|---|
| 1. Applicant | Astra Merck Inc. |
| 2. Patent No.<br>Expiration Date | 4,636,499<br>May 30, 2005 |
| 3. Type of Patent | Drug substance |
| 4. Name of the Patent Owner | Aktiebolaget Hässle |
| 5. Representative authorized to receive notice of patent certification under section 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. |

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

| | |
|---|---|
| 1. Applicant | Astra Merck Inc. |
| 2. Patent No.<br>Expiration Date | 5,093,342<br>February 2, 2010 |
| 3. Type of Patent | Method of use |
| 4. Name of the Patent Owner | Aktiebolaget Hässle |
| 5. Representative authorized to receive notice of patent certification under section 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. 5,093,342 covers a method of use of omeprazole (PRILOSEC®), i.e., treatment of H. pylori-associated Duodenal Ulcer. 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.<br>Expiration Date | 5,599,794<br>February 4, 2014 |
| 3. Type of Patent | Drug product and method of use |
| 4. Name of the Patent Owner | Astra Aktiebolag |
| 5. Representative authorized to receive notice of patent certification under section 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. 5,599,794 covers the formulation, composition, and method of use of omeprazole (PRILOSEC®), i.e., H. pylori-associated Duodenal Ulcer. 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.<br>Expiration Date | 5,629,305<br>February 4, 2014 |
| 3. Type of Patent | Drug product and method of use |
| 4. Name of the Patent Owner | Astra Aktiebolag |
| 5. Representative authorized to receive notice of patent certification under section 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. 5,629,305 covers the formulation, composition, and/or method of use of omeprazole (PRILOSEC®), i.e., for treatment of H. pylori-associated Duodenal Ulcer. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act: Application No. 19810 001.

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

# ITEM 14

# PATENT CERTIFICATION

NOT APPLICABLE

This application is not a 505(b)(2) application, therefore, the Patent Certification as described under 21 CFR §314.50 is not required.

**EXCLUSIVITY SUMMARY for NDA # 19-810 SUPPL #058**

**Trade Name Prilosec Generic Name Omeprazole**

**Applicant Name AstraZeneca HFD-180**

**Approval Date February 23, 2004**

**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 /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

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

YES /_X_/ NO /___/

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # /

NDA # 21-229 Omeprazole OTC

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 /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

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

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

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 /_X_/

***This was the 6th cycle review for this supplement that originally sought to change the pregnancy category from C to B in the label, this was denied and the last several review cycles have been labeling changes only without any new clinical data review.**

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

2. A clinical investigation is "essential to the approval" if the

Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ 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 #

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 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

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

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

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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: _____

_____

_____

Monika Houstoun
Signature of Preparer Date May 26, 2004

Title: Regulatory Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-180/Division File
HFD-180/RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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

/s/

Joyce Korvick
6/7/04 11:55:04 AM

## 1.0 DEBARMENT CERTIFICATION

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

Division of Gastrointestinal & Coagulation Drug Products

# REGULATORY PROJECT MANAGER REVIEW

**Application Number:** NDA 19-810/SLR-003 and SE8-058

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

**Sponsor:** AstraZeneca LP

## Material Reviewed

**Submission Date:** December 22, 2003

**Receipt Date:** December 23, 2003

**Background and Summary Description:** Prilosec Delayed-Release Capsules was approved under NDA 19-810 on September 14, 1989. It is currently indicated for the treatment of duodenal ulcer, gastric ulcer, symptomatic gastroesophageal reflux disease (GERD), erosive esophagitis, maintenance of healing of erosive esophagitis, and pathological hypersecretory conditions.

NDA 19-810/SLR-067 was submitted November 15, 1999, received November 16, 1999, and provides for the addition of "blurred vision" and "[redacted] irritation" to the **ADVERSE EVENTS** section of the package insert and was approved on October 9, 2003.

NDA 19-810/SLR-080 was submitted as a Changes Being Effected (CBE) on April 9, 2003, received April 11, 2003, and provides for changes to the **PRECAUTIONS, Drug Interactions** section, specifically, drug interactions related to warfarin. This supplement was submitted in response to a December 16, 2002 letter from the Division requesting the inclusion of class labeling for proton pump inhibitors regarding potential drug interactions with warfarin and was approved on October 9, 2003.

NDA 19-810/SLR-003 was submitted on November 6, 1989, received November 7, 1989, and provides for the [redacted] **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section of the labeling regarding a primary malignant tumor seen in one rat. The current resubmission is dated December 22, 2003, received December 23, 2003, and is the 6th review cycle for this supplement.

NDA 19-810/SE8-058 was submitted with Final Printed Labeling on October 7, 1998, received October 7, 1998, and provides for revisions to the **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy and Nursing Mothers** subsection of the **PRECAUTIONS** section of the labeling including a change in pregnancy category from C to B. In review cycle 2, it was decided to maintain pregnancy category C. The current resubmission is dated December 22, 2003, received December 23, 2003, and is the 6th review cycle for this

supplement.

NDA 19-810/SLR-003 and SE8-058 were submitted together.

**Review**

Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines. The following revisions were noted.

Package insert

The submitted FPL, identified as "9199410, 640004-40 rev. 12/03" was compared to the package insert, identified as "9194138, 640004-38 rev. 3/03", which was approved with SLR-067 and 080 on October 9, 2003.

1. The **Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy** subsection of the **PRECAUTIONS** section contains the following revisions:

- The first sentence in the first paragraph contains the following revisions:

From:
"In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole."

To:
In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day ~~(approximately 4~~ about 0.7 to ~~352~~ 57 times ~~the~~ a human dose, ~~based~~ of 20 mg/day, as expressed on a ~~patient weight of 50 kg and a human dose of 20 mg~~ body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole.

**Comment:**

**These changes were discussed in a conversation between Ms. Monika Houstoun,**

**Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- The forth sentence in the first paragraph contains the following revisions:

From:
"In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug."

To:
"In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day ~~(approximately 35~~ about 6 times ~~the~~ a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- The eighth sentence in the first paragraph contains the following revisions:

From:
"An unusual primary malignant tumor in the stomach was seen in one rat (2%)."

To:
"~~An unusual primary malignant tumor in the stomach~~ Gastric adenocarcinoma was seen in one rat (2%)."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- An eleventh sentence was added in the first paragraph as follows:

"In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found

in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males or females at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis)."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- The first sentence in the second paragraph contains the following revisions:

From:
"Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration."

To:
"Omeprazole was ~~not mutagenic~~ positive for clastogenic effects in an *in vitro* ~~Ames *Salmonella typhimurium*~~ human lymphocyte chromosomal aberration assay, ~~an~~ in ~~*in vitro* mouse lymphoma cell assay and an~~ one of two *in vivo* ~~rat liver DNA damage assay. A~~ mouse micronucleus ~~test at 625~~ tests, and ~~6250 times the human dose gave a borderline result, as did~~ in an *in vivo* bone marrow ~~chromosome~~ cell chromosomal aberration assay."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- The second sentence in the second paragraph contains the following revisions:

From:
"A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative."

To:
"Omeprazole was negative in the *in vitro* Ames test ~~A second~~, an *in vitro* mouse ~~micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.~~ lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

- The first sentence in the third paragraph contains the following revisions:

From:
"In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals."

To:
"~~In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.~~ Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted.**

2. The **Pregnancy** subsection of the **PRECAUTIONS** section contains the following revisions:

- The first paragraph has been deleted and new text proposed as follows:

From:
"In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to

172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole"

To:

"~~In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole~~ There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[2]"

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted. These changes were recommended in the 4th review cycle by the Pregnancy Labeling Team on October 28, 2002 and are acceptable.**

- The second through the fifth paragraphs were inserted as follows:

"Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole

during pregnancy.[3] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[4] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[5] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia. Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted. These changes were recommended in the 4th review cycle by the Pregnancy Labeling Team on October 28, 2002 and are acceptable.**

- The first sentence of the sixth paragraph contains the following revisions:

From:
"Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

To:
"Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted. These changes were recommended in the 4th review cycle by the Pregnancy Labeling Team on October 28, 2002 and are acceptable.**

3. The **Nursing Mothers** subsection of the **PRECAUTIONS** section contains the following revisions:

- The first paragraph under the subsection **Nursing Mothers** contains the following revisions:

From:
"It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

To:
"~~It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk~~ Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Choudary, Supervisory Pharmacologist, on February 11, 2004. In that discussion, Dr. Choudary indicated the changes are acceptable as submitted. In the Medical Officers review dated February 4, 2004, these changes were found acceptable.**

2. In the **HOW SUPPLIED** Section, the following NDC numbers were deleted:

- For the 10 mg strength:

**NDC** 0186-0606-68 bottles of 100
**NDC** 0186-0606-28 unit dose packages of 100"

- For the 20 mg strength:

**NDC** 0186-0742-28 unit dose package of 100

- For the 40 mg strength:

**NDC** 0186-0743-28 unit dose packages of 100

**Comments:**

**These changes were discussed in a conversation between Ms. Monika Houstoun, Regulatory Project Manager and Dr. Raghavachari, Chemistry Reviewer, on February 12, 2004. In that discussion, Dr. Raghavachari indicated the changes are acceptable as submitted.**

## Conclusions

The submitted labeling is acceptable per the medical Officer review dated February 4, 2004 and an approval letter should be issued to the sponsor.

Monika Houstoun, Pharm.D.
Regulatory Health Project Manager

Jasti Choudary, BVSc., PhD.
Supervisory Pharmacologist

Ramesh Raghavachari, PhD.
Chemistry Reviewer

Brian Strongin, RPh., MBA.
Chief Project Management Staff

Draft: MHoustoun/February 6, 2004,
Revised/Initialed: JChoudary/ February 11, 2004; RR/February 11, 2004; SD/February 11, 2004
Final: MH/February 19, 2004
Filename: c:\mydocuments\N 19-810\N 19810 S-003 and S-058-labeling-review.doc
RPM Review

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/s/

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Monika Houstoun
2/19/04 07:43:55 AM
CSO

Jasti Choudary
2/19/04 08:05:05 AM
PHARMACOLOGIST

Ramesh Raghavachari
2/19/04 09:09:02 AM
CHEMIST

Brian Strongin
2/19/04 01:29:08 PM
CSO

followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

**RECOMMENDATION: The proposed revisions under PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility, should be reviewed by the Pharmacology Reviewer.**

**Pregnancy**
**Omeprazole**
*Pregnancy Category C*

**RECOMMENDATION: The proposed revisions under PRECAUTIONS, Pregnancy should be reviewed by the Medical Officer.**

**Conclusions**

1. The Pharmacology Reviewer should review the sponsor's August 16, 2001 proposed revisions to PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility section of the package insert.

2. The Medical Officer should review the sponsor's August 16, 2001 proposed revisions to the PRECAUTIONS, Pregnancy section of the package insert.

3. The final printed labeling should include the revisions approved in SLR-073 on October 30, 2001 regarding administration of the granules in applesauce. These revisions appear in the CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism: Omeprazole, PRECAUTUIONS, Information for Patients, and the DOSAGE AND ADMINISTRATION sections of the currently approved package insert.

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

Joyce Korvick, M.D.
Deputy Director

cc:
Original NDA 19-810/SE8-058
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/H.Gallo-Torres
J.Choudary
drafted: M.Walsh 1/17/02
initialed by: H.Gallo-Torres 1/18/02
J.Korvick 1/23/02
filename: N19810.S-058.Labeling.review.Februrary-2002.doc

PM REVIEW

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/s/
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Maria Walsh
1/24/02 08:46:40 AM
CSO

Joyce Korvick
1/25/02 03:26:28 PM
MEDICAL OFFICER

Walsh

**MEMORANDUM**

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

**DATE:** October 16, 2000

**TO:** NDA 19-810/S-058
Prilosec (omeprazole) Delayed-Released Capsules

**FROM:** Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

**SUBJECT:** Epidemiology Consult Reviews

AstraZeneca submitted NDA 19-810/SE8-058 on October 7, 1998 for proposed revisions to the package insert under PRECAUTIONS. *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy:* and *Nursing Mothers.* These revisions included a change in the *Pregnancy Category* from *C* to *B.* This supplement was not approvable on October 7, 1999. The sponsor responded to the not approvable letter on August 4, 2000.

The Division of Gastrointestinal and Coagulation Drug Products consulted the Division of Drug Risk Evaluation 2 on June 8 and August 15, 2000 and requested "comment on the feasibility and design characteristics of a large, prospectively designed epidemiological study of women to omeprazole during pregnancy. Outcomes of interest include induced abortions, spontaneous abortions, miscarriages and relative risk for congenital abnormalities (in particular, cardiac septal defects)."

In response to the consult requests, attached are three epidemiology consult reviews from the following Special Government Employees:

Samuel Shapiro, M.D., Boston University
Lewis B. Holmes, M.D., Massachusetts General Hospital
Adolfo Correa, M.D., Ph.D., Center for Disease Control and Prevention

cc:
Archival NDA 19-810/S-058
HFD-180/Division File
HFD-180/RPM/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
M.Avigan
S.Kress
J.Choudary

Filename: C:\My Documents\19810.S058.October-2000.memo.consult.reviews.doc

**MEMORANDUM**

# Risk of Pregnancy-related Outcomes in Relation to in-Utero Exposure to Omeprazole

Samuel Shaprio, MB, FRCP(E)
Emeritus Director, Slone Epidemiology Unit, Boston University
Visiting Professor of Epidemiology, Columbia University

August/September

Introduction

I have been asked by the FDA to address concerns about pregnancy-related adverse outcomes in relation to omeprazole exposure. My specific remit is as follows:

"The agency has reviewed...three epidemiological studies and finds these data inadequate to show that omeprazole does not increase the risk of abnormalities when administered during the first trimester of pregnancy or that omeprazole has no effect on the rates of miscarriage or growth disturbances. Please comment on the design characteristics of a large, prospectively designed epidemiological study of women exposed to omeprazole during pregnancy. Outcomes of interest include induced abortions, spontaneous abortions, miscarriages [sic], and relative risk for congential anomalies (in particular, cardiac septal defects)."

As background I have been provided with copies of the three epidemiological studies, together with FDA in-house critiques by three reviewers. Some of the toxicological and teratological evidence in rats and rabbits, together with comments by one reviewer have also been provided. Finally, I have been provided with additional documentation submitted on August 4, 2000 by AstraZeneca LP to the FDA in response to the receipt of a "not-approvable" letter.

Among other things, the new documentation contains one as yet unpublished epidemiological study from Sweden. The study has augmented the number of omeprazole recipients in the data base, previously analyzed by Kallen in Sweden, to a total of 982. The data were confined to recipients of omeprazole; there was no external comparison group. Instead, outcome rates were compared between those exposed in the first trimester, and those exposed later. The studied outcomes included malformations, stillbirths, low weight and low Apgar score. No associations were observed, but with outcome numerators that ranged from only I-4 affected individuals identified in relation to exposures that took place after the first trimester (denominator = 131), the data were statistically unstable, and uninformative. The comparisons were also problematic in several other ways, and they will not be considered further, except to note that the overall observed malformation rate was 3% (27/853) for exposures in the first trimester, and the 3% (4/129) for later exposures. These rates are consistent with expected rates in the population at large, but in the absence of an appropriate comparison group they are of limited interpretability.

For the remaining three studies, I will not undertake yet another study-by-study critique, but rather first give an overview of the evidence, and of the general issues. Against that background, I will then make recommendations for post-marketing surveillance, as requested by the FDA.

The epidemiological evidence

Abortions. One of the of the three epidemiological studies (Lalkin et al) has provided limited data on induced and spontaneous abortions. I can see no reason to study induced abortion as an outcome, except inasmuch as it may be necessary to record its occurrence in order to properly assess the risk of spontaneous abortion. There may, for example, be problems of misclassification of the outcome that could conceivably bias or confound the analysis. Nevertheless, with very limited data, Lalkin et al observed similar rates of induced abortion among gravidae treated with omeprazole, histamine blockers, and among nonexposed gravidae.

The study of Lalkin et al was also the only one to provide data on the occurrence of spontaneous abortions. Based on reasonably stable numerators the abortion rates were 14% (16/113) in the omeprazole-exposed gravidae, as against 8% ((/113) in each of the other two comparison groups. However, 2 of the omeprazole recipients who aborted had scleroderma, and one received cytotoxic drugs. If they were excluded, as they had to be, the exposure rate became 10%, and similar to the rates observed in the non-exposed the comparison groups. Lalkin et al did not state whether there were cases that qualified for exclusion among gravidae not exposed to omeprazole, but presumably, if there had been any they would have been mentioned.

As a conceptual matter, spontaneous abortions are exceedingly difficult to study because of the following problems: a very high proportion of spontaneous abortions, 50% or more, are associated with chromosomal abnormalities—lethal abnormalities are probably the cause of most abortions, and in an adequate study design they should be identified; since abortions occur early, the recorded time of exposure to the suspect agent must clearly antedate the onset of the abortion; if chromosomal anomalies are at issue, the exposure of interest must take place during fertilization; for cultural reasons there can be considerable misclassifications between spontaneous and induced abortions, introducing the potential for major sources of bias and confounding; a substantial proportion of abortions, especially early abortions, may escape detection, again introducing the possibility of bias. These considerations have major implications for adequatee study design (see below).

Rodriguez et al explicitly excluded spontaneous and induced abortions in their study, presumably because they were aware of these issues, and lacked the data to study them properly. In one other study (Kallen) they were also not evaluated as outcomes. I agree with these decisions. If the risk of spontaneous abortion is to be properly evaluated, an ad hoc case-control study is needed in which all of the above considerations are fully taken into account, and allowed for (see below).

To sum up, there are no epidemiological data to suggest an increased risk of spontaneous abortion in omeprazole recipients, but the date are extremely limited.

Congential anomalies.

All three studies have evaluated the overall risk of congential malformations by comparing cohorts of women exposed to omeprazole with cohorts of non-exposed women. Particulars of the studies have varied, but numbers exposed to omeprazole in the first trimester were 262 (Kallen et al; Swedish data base: retrospective cohort study), 113 (Lankin et al; multinational prospective cohort study), and 134 (Rodriguez et al; data-based retrospective cohort study, United Kingdom, and Italy). Total malformation rates in the three studies were 3%, 4%, and 4% respectively. These rates did not differ significantly from the rates in the various comparison groups, which included, depending on the study, persons treated with histamine$_2$ blocking drugs, or persons to histamine suppressing drugs. Rates did not vary significantly when comparisons were confined to major malformations. In the most methodologically adequate of the three studies (Rodriguez et al), the relative risks for omeprazole, cimetidine, and rantidinine, relative to nonexposed gravidae, were 0.9 (95% CI 0.3, 2.2), 1.2(0.6, 2.3), and 1.4 90.8, 2.4).

In each of these studies individually, the numerators were small, and the upper 95% confidence limits did not exclude more than a doubling of the overall risk of congential anomalies. The studies can also be critized on other grounds, such as inadequate control of confounding. However, none of the studies had major methodological shortcomings. Taken together, I interpret the data across the studies as providing reasonably reassuring evidence to suggest that omeprazole does not increase the overall risk of congenital anomalies, or of major anomalies. Moreover, without formally combining the data, which would be improper, it is reasonable to judge that a large study would probably confidently exclude an upper confidence limit well below 2.0.

This conclusion should not be taken to imply that the studies were perfect. The FDA in-house criticisms have pointed out, for example, that they lacked precision on the timing and duration of exposure. Precise data are always preferable to imprecise data; otherwise misclassification may obscure associations. However, for omeprazole there was probably little variation in the dosage or duration of treatment, and the information that exposure took place in early pregnancy, while not ideal, was probably adequate. In addition, on the positive sides these studies had considerable strengths in the precision with which exposure was recorded as a yes/no variable, with minimal misclassification. And still further, the computerized birth defects analyzed in one of them (Rodriguez et al have previously been shown to be valid by inspection of the medical records.

Nor should this conclusion be taken to imply that that an increased risk of birth defects can be ruled out. Contrary to what is claimed by the sponsor reassurance about the overall malformation rate does not provide reassurance about the risk of specified birth defects. While known teratogens may cause a range of malformations, they tend to be strongly associated with specific sentinel malformations. For such malformations the

incidence may be as low as 1 in 1,000, or even 1 in 10,000, or less. Thalidomide, for example, is associated most prominently with phocomelia; accutane with craniofacial anomalies; tetracycline with damage to the teeth; and so on. Obviously, the published studies have lacked the statistical power needed to detect associations for outcomes with such low rates. Case-control methods would be essential to evaluate them (see below).

One of the FDA reviewers has argued that the observation of 2 cardiac septal defects among the omeprazole-exposed gravidae yields a relative risk of 7.6 (95% CI 1.3, 45), and 2 cases of hypospadias among cimetidine-expose yields an estimate of 13 (1.2, 145). The recording of septal defects may be based on nothing more than the observation of cardiac murmurs; depending on their location the embryological mechanisms that result in different septal defects can vary widely—they cannot be lumped together; a numerator of only 2 is too fragile to be meaningful; the association has been identified in the course of multiple stratification in which associations would be expected to arise by chance. Analogous considerations apply to hypospadias, the diagnosis of which, in addition, can vary considerably among observers, especially during the first months after birth when there is urinary and fecal incontinence. Without detailed and standardized evaluation, defect by defect, risk estimation for cardiac defects and hypospadias is inappropriate. In my judgement the associations mentioned in the FDA review do not constitute evidence to suggest a possible increased risk of cardiac septal defects in omeprazole users or of hypospadias in cimetidine users.

To sum up, I interpret the data across the studies as reassuring evidence to suggest that if omeprazole increases the risk of any specific congenital anomalies, that increase is not sufficient to result in a discernible increase in the overall incidence of birth defects among exposed infants. Further cohort studies would have to be unrealistically large to be informative regarding specific defects. In addition, there are no experimental or epidemiological data which indicate what specific defects, if any, should be studied. Put another way, there are no a priori grounds to single our cardiac septal defects, or any other specific defects, for study. Finally, if any specific defects were to be studied the only realistic approach would be by means of case-control studies (see below).

Preterm delivery and other outcomes.

Rodriguez et al observed rates of preterm delivery before 37 weeks of gestation of 8%, 9%, 6%, and 7% among gravidae exposed to omeprazole, ranitidine, and cimetidine, and among nonexposed gravidae, respectively. Lalkin et al observed rates of 9%, 16%, and 8% in gravidae exposed to omeprazole and histamine blockers, and in nonexposed gravidae, respectively. The numerator data were reasonably stable in all the comparisons. With the exception of the one 16% rate for histamine blocker recipients in one study, these rates are closely similar. Taken together, they constitute good evidence to suggest that omepraole does not increase the risk of premature birth. By inference they also suggest that omeprazole is unlikely to have effects such as growth retardation, although that conclusion must be considered more tentative. Rodriguez et al also had data on

Future be generated by case reports. However, at present there are no hypotheses. If FDA disagrees with my views concerning cardiac septal defects, these, properly classified in subgroups based on underlining embryological mechanisms, can be selected for study. Also, in the absence of any specific hypotheses, specific malformations can be monitored to a limited extent through case-control surveillance data bases such as those operated by the . Possibly, other data basses, such as those operated by the CDC in Atlanta, or by the could also be utilized. All relevant drugs, not only omeprazole, should be monitored.

3. If FDA recommends further study of the risk of spontaneous abortion, a well designed case-control study will again be necessary; and again all of the relevant drugs should be studied. The methods for studying abortion risk are well developed, and there are experienced investigators in this area.

Concluding Comments.

In conclusion I reiterate my main points. Based on the experimental evidence, I judge that there is no biological plausibility to the general hypothesis that omeprazole has adverse effects on pregnancy outcomes. The associations that have been observed in the experimental data all appear to have a mechanism basis that is unlikely to be relevant to human beings. Epidemiologically, the existing evidence suggests that omeprazole does not increase the overall risk of malformations. However, as for most other drugs, the possibility that omeprazole increases the risk of specific malformations has not been excluded. Further evaluation of hypotheses concerning specific malformations, if deemed necessary, can only realistically be accomplished in case-control studies, or by case-control surveillance. The risk of spontaneous abortion can be evaluated only in an ad hoc case-control study. Outcomes such as short-term delivery, and related outcomes, can probably be adequately evaluated by further analysis of existing or relatively easily accessible data.

Large scale prospective studies are not needed. If they are nevertheless undertaken, they can shed further light on overall malformation risk, and on other relatively common outcomes such as short term deliveries, and perhaps a few related entities. They will not be of value in the assessment of the risk of specific malformations.

In my view, there is no need to single out omeprazole for more intensive post-marketing surveillance than any other drug is subjected to. If such surveillance is nevertheless deemed necessary, it should be applied symetrically to omeprazole and to other $H_2$ blockers.

TO: Mary Dempsey, Project Manager (dempsey@cder.fda.gov)
Food and Drug Administration

FROM: Lewis B. Holmes, M.D.
Genetics & Teratology Unit, Pediatric Service
Massachusetts General Hospital, Boston, MA 02114

CC: Evelyn M. Rodriguez, M.D., M.P.H.
Dr. Mary Willy

RE: Analysis of 20 adverse event reports concerning exposure to omeprazole during pregnancy

DATE: September 11, 2000

These are the 20 reports I was asked to evaluate, which I have outlined as to period of exposure and phenotype. I have listed them chronologically, by date of the infant's birth:

| Report Number | Infant DOB | Date of Report | Exposure to Omeprazole | Phenotype of Infant | Significant Other |
|---|---|---|---|---|---|
| 1. WAES92050713 | | 12-18-92 | 8d., starting at about 3.5 wks GA | "mild random Duane's syndrome | |
| 2. WAES92060147 | | 9-11-92 | 18, wks to 32 wks GA | Hydranencephaly; severe microcephaly; contracture | Mother was Class C Insulin-dependent diabetic |
| 3. 19950900045 | | 9-21-95 | 2-91 (presumably treated one month) | Severely handicapped infant | Infant has 2 complex chromosome rearrangements |

| | | | | |
|---|---|---|---|---|
| 4.<br>WAES93030842 | 6-10-93 | 7 d. postconception throughout pregnancy | Sacral lipomeningocele; cleft lip and palate | |
| 5.<br>WAES93061143 | 7-8-93 | From conception to 8 weeks GA | Anencephaly | |
| 6.<br>19940700090 | 11-15-94 | From week 6 to 13 GA | Anencephaly | |
| 7.<br>19940900104 | 10-3-94 | Approximately 6 to 13 weeks GA | products of conception removed at 13 weeks GA; noted to have "stopped development" | |
| 8.<br>19950200046 | 8-22-95 | First 4 weeks postfertilization | "hypoplastic heart" (fatal) | |
| 9.<br>19951100030 | 11-17-95 | 30 wk GA to delivery | Pyloric stenosis | |
| 10.<br>19951200114 | 12-27-95 | Not clear | Anencephaly | Positive family history for anencephaly and spina bifida |
| 11.<br>19950600134 | 11-13-95 | Last 3 months of pregnancy | Severe hypoglycemia and metabolic acidosis (no malformations described) | |
| 12.<br>19950900177 | 11-6-95 | Not clear | Cleft palate | |
| 13.<br>19951000273 | 11-7-95 | ? presumably first trimester | Anencephaly | Published case reports; 2 births to a woman presumably taking omeprazole throughout |
| 14.<br>19951000270 | 11-7-95 | ? presumably first trimester | Severe talipes | Same mother as case #13 |

| | | | |
|---|---|---|---|
| 15.<br>1996100099 | 10-22-96 | Part of first month post-fertilization | Small apical ventricular septal defect |
| 16.<br>19990700200 | 7-23-99 | First trimester | Maxillary mono-ostotic fibrous dysplasia |
| 17.<br>19961000189 | 11-1-96 | Began 1-15-96 (? First month) | "peromelia of left arm" |

| | | | | |
|---|---|---|---|---|
| 18.<br>19971000103 | 12-4-97 | Until pregnancy diagnosed; then restarted 5-28-97 | Oculo-auriculo-fronto-nasal syndrome | |
| 19.<br>B0049396 | 10-22-97 | First 8 weeks of gestation and from 21 weeks to delivery | "severe facial dysmorphism" | |
| 20.<br>19990100157 | 8-4-99 | First trimester | Anophthalmia and hydrops | Mother had surgery to treat obesity |

These are a very diverse group of outcomes. In considering whether any could have been caused by the exposure to omeprazole, I would add these qualifying comments for several of these cases:

1. "Mild, random Duane's syndrome". The Duane anomaly is a congenital eye movement disorder characterized by limitation in abduction and narrowing of the palpebral fissures. This has been identified as an effect of thalidomide, but not as an isolated finding. This type of outcome is not identified in newborn infants, as it is established only by a careful exam that requires the person's cooperation in following directions. It is not clear from the report that the finding persisted into childhood. I would not list this outcome as a major malformation.

2. The teratogenicity of maternal diabetes is known to produce a diverse group of major malformations. While some rare malformations are much more common in infants of diabetic mothers (IDM), there is no recognizable syndrome in many malformed IDM in contrast to infants affected by other maternal disorders that are teratogenic, e.g. maternal myasthenia or excessive alcohol consumption.

3. The report does not describe a specific phenotype and suggests that this infant had either a significant excess or deficiency (or both) of chromosome material. Chromosome abnormalities in the fetus have not been shown to have been produced by exposure to medication taken by the mother during pregnancy.

5. Pyloric stenosis is not a major malformation. It is caused by hypertrophy of muscle. While it has been tabulated in many epidemiologic studies as a "malformation", it is not a structural abnormality.

7. This fetus with anencephaly was exposed to omeprazole from weeks 6 to 13 of gestation, which would have been after a neural tube defect would have been visible (fourth week post fertilization).

8. This outcome is an elective termination of what would have been a spontaneous abortion. This can only be put in the context of spontaneous abortions which occur in about 15% of pregnancies. Since half of all spontaneous abortions are associated with a - chromosome abnormality, it is unfortunate that the results of such studies were not provided.

9. Presumably the term "hypoplastic heart" refers to "hypoplastic left heart" or "hypoplastic right heart", both of which are observed regularly in malformations surveillance.

11. "Severe hypoglycemia and metabolic acidosis" are not part of the spectrum of outcomes included in the definition of major malformations that I use in evaluating the effects of human teratogens.

15. Ventricular septal defects are the most common type of heart defects. As described, we do not know if this is a muscular type or a membranous type. The muscular type closes spontaneously. It is so common that it is not being considered a major malformation by the National Birth Defects Prevention Study, a CDC-funded eight state study of the causes of selected major malformations identified from the surveillance of newborn infants.

16. "Maxillary mono-ostolic fibrous dysplasia" is an unusual outcome. Further information would be useful. Is there another name for this infant's condition?

19. "Severe facial dysmorphism" is a non-specific term, which could refer to either malformations or deformations or both. More information would be very helpful.

20. One consequence of surgical treatment of obesity is vitamin deficiency. This has been suggested to be a risk factor in case reports of neural tube defects, but not in infants with anophthalmia to my knowledge.

Evaluation of reports:

In carrying out a review of outcomes like these it would be helpful to have inclusion and exclusion criteria for what is considered a significant "abnormality". Clearly human teratogens can produce a wide spectrum of phenotypic effects. The focus on the occurrence of major malformations is usually used as these are a known effect of many teratogens. Furthermore, these findings can be put in the context of what occurs in the general, unexposed population, with the question: does this occur spontaneously? Is there anything distinctive about this infant's phenotype? When outcomes other than major malformations are considered potential teratogenic effects, the reviewer needs a reference point to its frequency in the unexposed population.

Experience has shown that case reports, such as adverse event reports, cannot establish causality (ref. 1). However, one can ask whether the outcomes reported show phenotypes that are "atypical" or distinctive, as teratogenic drugs often produce recognizable patterns of major and minor anomalies.

Since inclusion/exclusion criteria were not provided for this review, I have used my own (ref. 2). I have used these in determining the frequency of major malformations in the surveillance of major malformations in a consecutive population of 200,000 newborn infants (ref. 3). We are also using these criteria in the North American AED (antiepileptic drug) Pregnancy Registry in which the teratogenic potential of all AED used in pregnancy are being evaluated.

I have drawn these conclusions for my review of these 20 reports:

1. I cannot consider any of the cases reported to be omeprazole-related. There is no known teratogenic effect of omeprazole. The outcomes reported reflect the types of malformations which occur spontaneously and illustrate the more severe end of the spectrum.

2. Several of these outcomes are not major malformations. In this group I include the infants with Duane's Syndrome, hypoglycemia and pyloric stenosis.

3. One outcome was analogous to a spontaneous abortion, and not a newborn infant with birth defects.

4. Two infants had co-existing problems, specifically maternal insulin-dependent diabetes mellitus and a complex chromosome abnormality (not specified), which are more likely causes of the outcome described.

5. Almost all of the infants described had significant exposures to other drugs. While none reported is recognized as a human teratogen, they have not been studied well enough in human pregnancies to establish their apparent safety.

6. Ideally one could assess the dose and period of exposure, but the information presented on this small number of cases is too limited and does not include a wide range of doses. However, it was noted appropriately that the exposure in one pregnancy occurred after the malformation (anencephaly) would have been present in the exposed embryo/fetus.

References:

1. Shepard TH. "Proof" of human teratogenicity. Teratology 50:97-98, 1984.

2. Holmes LB. Need for inclusion and exclusion criteria for the structural abnormalities recorded in children born from exposed pregnancies. Teratology 59:1-2, 1999.

3. Nelson K, Holmes LB: Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med 320:19-23, 1989.

# Electronic Mail Message

**Date:** 9/6/00 2:57:39 PM
**From:** Correa, Adolfo ( aic8@cdc.gov )
**To:** Willy, Mary E. (FDA) ( WILLYM@A1 )
**To:** Dempsey, Mary J. (FDA) ( DEMPSEYM@A1 )
**To:** Rodriguez, Evelyn M. (FDA) ( RODRIGUEZE@A1 )
**Cc:** Correa, Adolfo ( aic8@cdc.gov )
**Cc:** Erickson, Dave ( jde1@cdc.gov )
**Subject:** requested review of pregnancy-related outcomes

Attached please find the following:

1) Review of epi papers
2) Review of reports of adverse events with classification table (excel file)
3) Comments on cohort study

<<omeprazolepapers.doc>> <<fdacohort.doc>> <<adverse event reports.doc>>
<<FDACASES2.xls>>

Please let me know if you have any questions.

Thank you for the opportunity to assist you with this interesting and portant problem.

olfo Correa, MD, PhD
Division of Birth Defects, Child Development, and Disability and Health
National Center for Environmental Health
Centers for Disease Control and Prevention
4770 Buford Highway, NE MS F-45
Atlanta, GA 30341

(770) 488-7164 / Fax: (770) 488-7197
acorrea@cdc.gov

## Review of Epidemiological Studies on Omeprazole and Pregnancy Outcomes

## 1. Källén B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. Brit J Obstet and Gynaecol 1998;105:877-81.

### 1.1. Summary

This study examined the relation between use of acid-suppressing drugs early in pregnancy and risk of congenital malformations using a retrospective cohort design. The study population consisted of offspring to Swedish pregnant women born between 1995 and early 1997 (n ~200,000). The main source of data was the Swedish Medical Birth Registry, which consists of a database of computerized records on antenatal care and other prenatal factors (e.g., smoking and drug use), delivery records, and pediatric examinations of all newborns, collected prospectively in a standardized format. This registry was the source of the study cohort (mothers who had used any acid-suppressing drugs after becoming pregnant and before the first antenatal visit [1st trimester exposure]), data on drug use, and cases of congenital malformations. Another data source was the Registry of Congenital Malformations, which was linked to the Medical Birth Registry to ascertain additional cases. Data on drug use stored in this registry include information on proprietary name, dosage, and sometimes when the drug was used. Data on drug use, collected by interview by midwives at the time of the first antenatal clinic visit (1st trimester), were used to identify the study cohort: pregnant women who used proton-pump blockers (n=275), $H_2$-receptor antagonists (n=255), or both types of drugs early in pregnancy (n=20). Cases of malformations were infants in the Medical Birth Registry with conditions classified with an ICD9 code for congenital malformations or infants who had been reported to the Registry of Congenital Malformations. Cases were ascertained among stillbirths and in early postnatal life. Infants with cardiovascular defects were checked against a register of infants with congenital heart defects diagnosed in infancy. Congenital malformations diagnosed prenatally and resulting in pregnancy termination were excluded. Risk ratios estimates were based on observed to expected ratios (i.e., comparisons with all births in the Medical Birth Registry), stratified by year of birth, maternal age, parity, and smoking habits early in pregnancy. Comparisons between different drug groups and analysis of certain population characteristics were made with odds ratios (OR).

Compared to women in the general population, women using acid-suppressing drugs in early pregnancy in this cohort were more likely to be older, primiparous, and smokers. Among the cohort of 547 exposed pregnancies, there were 17 offspring with malformations identified in the Medical Birth Registry, for a crude prevalence rate of 3.1% (95% CI 1.8-4.9), compared to a crude rate of 3.9% among all infants. The OR for congenital malformations in the drug exposed infants compared to all infants in the registry stratified by year of birth, maternal age, parity, and maternal smoking early in pregnancy was 0.72 (95% CI 0.41-1.24). The corresponding OR for infants after only proton-pump blocker use was 0.91 (95% CI 0.45-1.84), after only $H_2$-receptor antagonists use 0.46 (95% CI 0.17-1.20), and after omeprazole use 0.59 (95% CI 0.28-1.25). The authors report that there was no difference in the total proportion of malformations among the five groups (omeprazole, lansoprazole, cimetidine, ranitidine, and omeprazole and ranitidine combined) but provide no data on the denominators for these five groups.

Many of the malformations were minor. In the proton pump blocker group, there were six infants with congenital heart defects (three VSD, one ASD, one PDA in a term baby, one unspecified), one with urethral valve, one with undescended testis, one with an unspecified facial anomaly, and one with Down's syndrome. In the $H_2$-receptor antagonist group there was one infant with a cardiovascular defect (unspecified), one with unilateral hydronephrosis diagnosed prenatally, one with a non-immune hydrops, one with a cerebral arterio-venous malformation, one with undescended testis, one with an

unstable hip, and one with hypospadias. In the group who used both omeprazole and ranitidine, there was one case of hypospadias.

The authors conclude that, although a teratogenic effect of these drugs cannot be ruled out, the individual risk after exposures during the first trimester seems negligible.

1.2. Strengths and Limitations

1.2.1. Strengths

The cohort design allowed an independent assessment of both exposure and outcome, minimizing the potential for systematic errors on exposure and outcome classification. Since this study was based on the Medical Birth Register, there were no refusals to participate, minimizing the potential for selection bias. Drug use data were collected prospectively, in a standardized manner, and included information on drug use during the first trimester, the period of higher susceptibility to the effects of teratogens for most organ systems. This allowed identification of well-defined and mutually exclusive exposure groups. Statistical analysis took into account year of birth, maternal age, parity and smoking habits. This helped minimized potential confounding by these variables. Finally, the authors acknowledge that the size of the study does not allow the exclusion of an increased risk of teratogenicity from omeprazole for specific defects.

1.2.2. Limitations

One limitation of this retrospective cohort is that the Medical Birth Register, which served as the source of this cohort, had no information on spontaneous abortions. This study, therefore, could not rule out an effect of omeprazole on spontaneous abortions.

The authors provide no information on the proportion of exposed pregnancies that may have had prenatal ultrasound, the proportion of pregnancies with prenatally diagnosed cases of malformations, or the proportion of such pregnancies that were terminated. The absence or low frequency of some of the more common major malformations (e.g., anencephaly, Down's syndrome, gastrointestinal anomalies) in a cohort of high risk women, suggests that prenatal detection and pregnancy termination may have occurred in this cohort. If prenatal diagnoses and pregnancy terminations occurred more frequently among women who used omeprazole early in pregnancy than among other groups of women, the rate of malformations among offspring to such women would be underestimated. This could well explain the lower rate of malformations in the study cohort compared to the rate of malformations in the Medical Birth Register and the low prevalence of major malformations in the study cohort. Therefore, it is difficult to exclude the possibility that the results are an artifact of selective pregnancy terminations in the exposed group.

The authors provide limited information on the completeness of ascertainment of cases of malformations in the Medical Birth Register. A recent publication based on data from the same Medical Birth Register (Wennerholm et al, Incidence of congenital malformations in children born after ICSI. Human Reproduction, 2000;15:944-8) suggests that this register may miss up to a third of the malformations subsequently found in the Register of Congenital Malformations. This under ascertainment could explain the low prevalence of

major malformations in this cohort. The lack of information on the basis of the diagnoses of congenital malformations makes it difficult to assess the accuracy of the diagnoses, and of the classification of cases in this study. The fact that the cases of ventricular septal defects had not been evaluated at the Child Cardiology Register suggests that such cases might have been mild and that the classification of cases was subject to error. Errors in the classification of cases as non-cases and of non-cases as cases may have attenuated differences in rates of malformations between the comparison groups.

Inclusion of ill-defined conditions and minor anomalies as outcomes increased the sample size but may have been counterproductive. If omeprazole is associated with specific defects that originate in the first trimester, inclusion of infants with ill-defined conditions (e.g., facial anomaly, unspecified congenital heart defects) and of undescended testis and hypospadias in the analysis may have diluted any effects from exposure. Since hypospadias and descent of the testis do not occur until late in pregnancy, use of exposures that occur early in pregnancy may have resulted in misclassification of the more relevant exposures (i.e., late in pregnancy).

The authors provide no frequency distribution for congenital malformations in the reference population. In the absence of such a distribution, it is difficult to establish that the observed cases among the exposed are no different from the expected.

The reference group for estimation of odds ratios was not clearly defined. Did the reference group consist of all births in the Medical Birth Register? Or did it consist of the all births minus the study cohort? Use of the former reference group might have attenuated any effects from omeprazole.

One of the major limitations of this study is the size of the cohort. The study may have been of sufficient size to detect at least a moderate increase in the rate of all malformations in the cohort compared to all births (i.e., RR 1.65, power of 0.80, =0.05, 1-sided test). However, since exposure to most teratogens is likely to result in an increased risk of specific malformations rather than an increase in all malformations, this study may have lacked adequate power to rule out an increase in the risk of specific malformations from omeprazole use early in pregnancy.

## 2. Lalkin A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. Am J Obstet Gynecol 1998;179:727-30.

### 2.1. Summary

This cohort study examined whether omeprazole use during pregnancy was associated with an increased risk of malformations, spontaneous abortions, decreased birth weight, or perinatal complications. The study population consisted of pregnant women counseled early in pregnancy by one of four teratogen information centers: Motherisk (Toronto, Canada); Telefono Rosso (Rome, Italy); Service de Pharmaco-Toxicovigilance (Lyon, France), and Centro Regionale d'Informazione sul Farmaco (CRIF-Milan, Italy). At the initial consultation, such women were interviewed to elicit information on maternal demographic characteristics, medical and obstetric histories, indication for treatment and time of exposure, concurrent medications, and family history of birth defects. Shortly

after delivery, each woman was recontacted regarding pregnancy outcome, labor and delivery, and neonatal complications. Women exposed to omeprazole during pregnancy (n=113) were individually matched with two reference groups: pregnant women exposed to nonteratogenic drugs; and disease-paired controls who used histamine blockers for similar indications. Matching criteria were maternal age, smoking pattern, and alcohol consumption. The primary endpoint was the incidence of major malformations (i.e., those having an adverse effect on function or social acceptability). Secondary endpoints were pregnancy outcome, birth weight, rates of preterm delivery, and neonatal health problems.

Women from the four participating centers had similar reproductive, smoking and alcohol use characteristics. Exposure to omeprazole during the period of organogenesis (4-14 weeks of gestation) was reported by 89% of the mothers, and throughout gestation by 15 % of the mothers. Disease-paired controls reported fewer previous miscarriages than the nonteratogenesis controls. Women who used omeprazole during pregnancy were prescribed other agents more often than their disease-paired controls. The prevalence rates of major malformations in the omeprazole, disease-paired control, and nonteratogenic control groups were 4/78 (5.1%), 3/98 (3.1%), and 2/66 (3.0%), respectively. Among omeprazole exposed offspring, the major defects were ventricular septal defect (1), polycystic kidneys (1), ureteropelvic junction stenosis (1), and patent ductus arteriosus (1). Among disease-paired controls, the major defects were atrial septal defect (1), and ventricular septal defect (2). Among nonteratogenic controls, major defects were atrial septal defect (1) and developmental delay (1). The rates of spontaneous abortions in the omeprazole, disease-paired control, and nonteratogenic control groups were 16/113 (14%), 9/113 (8%), and 9/113 (8%), respectively. The rates of elective abortions in the omeprazole, disease-paired control, and nonteratogenic control groups were 6/113 (5%), 3/113 (3%), and 5/113 (4%), respectively. No differences were found for preterm delivery, mean birth weight, and gestational age at delivery or method of delivery. There were no differences in jaundice or the number of days in the intensive care unit between groups (data not shown). The authors conclude that there is no association between exposure to omeprazole and risk for major malformations, spontaneous abortions, decreased birth weight, or perinatal complications.

## 2.2. Strengths and Limitations

### 2.2.1. Strengths

The cohort design allowed ascertainment of various pregnancy outcomes and an independent assessment of both exposure and outcome, minimizing the potential for systematic errors on exposure and outcome classification. Although the study combined populations from four teratology information centers (Toronto, Rome, Milan, and Lyon), the four populations appeared to share similar reproductive and lifestyle characteristics (i.e., smoking and alcohol consumption habits). Drug use data were collected prospectively and included information on indication for treatment and time of exposure, concurrent medications, and family history of birth defects. Two reference groups were included in this study: one consisting of diseased-paired individuals and another of women who had taken drugs considered to be nonteratogenic. These reference groups were matched to the exposed group on selected potential confounders, including maternal age, maternal smoking and alcohol consumption habits. Another strength is the collection of data on and evaluation of several pregnancy outcomes. Lastly, the authors indicate the minimal excess risk for malformations and spontaneous abortions that their study can identify and acknowledge that their study does not have adequate power to detect a 3-fold increase in the rate of malformations.

2.2.2. Limitations

This study is based on a cohort of pregnant mothers counseled by teratogen information centers. This cohort includes mothers who took other medications other than omeprazole. However, this cohort does not include mothers who might have taken omeprazole but did not seek advice from the teratogen information services. Such a universe or reference population is not known and the period of births is not specified. Therefore, it is not possible to know how representative the cohort is of pregnant mothers who took omeprazole or any other medications during pregnancy. There is a possibility that pregnant women who took omeprazole during pregnancy and who might be more susceptible to adverse pregnancy outcomes from such exposures might have chosen not to call the participating centers for advice. From the information provided in the article, it is not possible to exclude this type of selection bias as a possible explanation for the study findings.

The authors provide no information on the calendar period of conception or birth for the subjects in this study. Although the exposed and reference groups are similar in maternal age, and alcohol and tobacco use, it is not clear that they are comparable on the year of birth and, therefore, on other potential confounders that might have varied over time, such as infections, diet, or use of multivitamin supplements.

Information on pregnancy outcome, labor and delivery, and neonatal complications was obtained from interviews of the mothers shortly after delivery. How successful this approach was in ascertaining all pregnancy outcomes, however, is unclear. Pregnancy losses early in pregnancy may go unrecognized, resulting in an underreporting of the true number of spontaneous abortions. Such underreporting could result in an underestimation of the rates of spontaneous abortions. The low rate of spontaneous abortions in the control groups (8% vs. an expected rate of at least 11%) suggests that underreporting of spontaneous abortions may have occurred in this study. If this kind of error occurred to the same extent in the exposed and reference groups, the power of the study to detect a difference in rates would be minimized. This may be one explanation for the findings on spontaneous abortions.

The definition and ascertainment of malformations were problematic. The study relied on a somewhat subjective definition of malformations (i.e., those having an adverse effect on either the function or social acceptability of the individual). This definition leaves a good deal of latitude for interpretation by those reporting the malformations, and may have resulted in a good deal of variation in reporting of malformations, with some malformations being underreported and some conditions being erroneously reported as malformations (e.g., developmental delay). In addition, interview data on the presence/absence of malformations and on the type of malformations can also be subject to error. Some malformations (e.g., some cardiac anomalies and syndromes) may be undiagnosed or misdiagnosed shortly after birth, particularly if assessments are not carried out with standardized methods. If nondifferential with respect to exposure group, such misclassification errors can result in attenuation of a difference in rates of malformations between study groups.

Although the authors provide information on the number of pregnancy losses in each comparison group, the authors provide no information on the proportion of pregnancies that

may have had prenatal ultrasound, the proportion of such pregnancies with prenatally diagnosed cases of malformations, or the proportion of pregnancies that were terminated due to the presence of a malformation. The authors provide information on the number of therapeutic abortions but not on the indications for such abortions or on whether the indications for such abortions were similar for the three comparison groups. If prenatal diagnoses and pregnancy terminations occurred more frequently among women who used opremazole early in pregnancy than among other groups of women, the rate of malformations among offspring to such women would be underestimated.

The comparison groups were limited in size. The authors indicate that the incidence rate of malformation in the omeprazole group did not differ from the rates in the control groups. This is partly true. The rate of malformations was slightly higher in the omeprazole group than in either control group (RR = 1.67, 95% CI 0.15-48.67), but the confidence interval was wide and included the null value. The lack of a statistically significant difference may have reflected no difference in risks but it may have also been due to the low prevalence of malformations and the limited size of the cohort. The fact is that this study only had limited power (i.e., 7%) to detect a 61% increase in risk of malformations. For spontaneous abortions, the same issue applies. There was a higher rate of spontaneous abortions in the omeprazole group compared to either of the control groups (RR = 1.74%, 95% CI 0.66-6.02), but the confidence interval was wide and included the null value. Exclusion of the mothers with scleroderma and lupus from the omeprazole group reduces but does not nullify this difference in rates of spontaneous abortions (RR=1.48, 95% CI 0.49-5.43). If one compares the rates of any adverse outcome (i.e., spontaneous abortion, elective abortion or birth defect), one can observe that there is a 71% increased rate of such an outcome in the omeprazole group than in the disease-paired group (RR =1.71, 95% CI 0.85-4.04). Again, this increase is not statistically significant, but it is consistent for the two control groups. Conversely, the rate of live births is 8% lower in the omeprazole than in the no-teratogen control group (RR= 0.92, 95% CI 0.78-1.06). This difference is not statistically significant, but it is consistent for the two control groups. This study only had a 31% power to detect such a difference in live births.

The authors indicate that only a minority of the patients (15%) reported omeprazole use throughout pregnancy. However, in the analysis of preterm delivery, birth weight, gestational age and method of delivery, they seem to include in the denominator (n=113) all patients, not only those exposed throughout pregnancy. Such inclusion would result in classification of patients who were unexposed in the last trimester as exposed to omeprazole and in the attenuation of any difference in rates in prematurity, low birth weight, and other neonatal health problems between the exposed and control groups.

## 3. Ruigomez A, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. Am J Epidermal 1999;150:476-81.

### 3.1. Summary

This study examined the relation between use of cimetidine, omeprazole, and ranitidine during the first trimester of pregnancy and prevalence of congenital malformations using a retrospective cohort design. Two computerized data sources were used to construct the study cohort: the United Kingdom

General Practice Research Database and the Italian Database. The study cohort included pregnancies among women less than 45 years of age for the period 1991 to 1996: 1,179 from the United Kingdom, and 1,057 from Italy. After ascertainment of last menstrual period dates, the authors identified women who received a prescription for cimetidine, omeprazole, or ranitidine during the first trimester of pregnancy and a control group of pregnant women who had not received these drugs during the first trimester. Women with spontaneous, elective abortions, or ectopic pregnancies were excluded. Outcomes included stillbirths (pregnancy losses after 27 weeks of gestation and pregnancy terminations due to a prenatal diagnosis of malformations) and congenital malformations (live birth or still with a structural defect detected prenatally, at birth, or during the first year of life. In the UK database, the authors reviewed the records of all cases and requested additional medical record information when the information for classification was inadequate). In the Italian cohort, the authors reviewed medical and vital records for children admitted to the hospital during infancy with an ICD9 code for a congenital malformation. Birth defects known to be genetic were excluded.

There were 20 stillbirths, and 2,261 live-born babies in both cohorts combined, 100 offspring being identified with a malformation (68 in the UK group and 32 in the Italian group). The overall malformation rate was 4.4%. The rates of malformations in the cimetidine, omeprazole, ranitidine, and control groups in the combined cohort were 11/237 (4.6%), 5/139 (3.6%), 20/330 (6.1%), and 64/1575 (4.1%), respectively. The relative risks for cimetidine, omeprazole, and ranitidine in both cohorts combined were 1.2 (95% CI 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CCI: 0.8, 2.4). respectively, compared with the control group. No specific grouping in the distribution of malformations was observed in any of the three exposed groups. Moreover, no relation was found between drug exposure and preterm delivery or growth retardation. The findings of this study suggest that use of acid-suppressing drugs during the first trimester of pregnancy is not associated with a major teratogenic risk.

## 3.2. Strengths and Limitations

### 3.2.1. Strengths

This study has the following strengths. The cohort design allowed an independent assessment of both exposure and outcome. This study was based on two different populations, in which there were computerized records of hospitalizations, births, and prescriptions, which allowed the construction of the study cohort and identification of outcomes. Drug use data were collected prospectively, and included information on drug use during the first trimester of pregnancy. Pregnancy terminations due to a prenatal diagnosis of a malformation were included in this evaluation. Ascertainment of cases of malformations was based on objective criteria (i.e., presence of an ICD9 code for a malformation in the database). In addition, there was an attempt to validate cases identified in the database in one of the two sub cohorts (Italian). Finally, the authors excluded infants with genetic syndromes, which would not be associated with drug exposure and would only dilute any effects from exposure.

### 3.2.2. Limitations

Since this study excluded spontaneous abortions, the study could not rule out an effect of omeprazole (or the other acid-suppressing drugs) on spontaneous abortions.

The case definition in this study was based on ICD9 codes present in the databases.

However, the authors provide no information on the types of evaluations that the ICD9 codes were based on. There was an attempt to validate cases in one of the databases (Italian), but there is no information provided on the number of false positives or on the number of cases that had to be reclassified. Although misclassification of one case for another may have no impact on the between-group comparisons of overall rates of malformations, it may result in attenuation of differences in rates for specific malformations.

There was a difference in case ascertainment in the UK and Italian cohorts, which may explain the difference in prevalence in malformations in the two cohorts. It would have been interesting to see the impact of such differences in the types of cases that were ascertained. Unfortunately, data on malformations were not presented separately for the UK and the Italian cohorts.

The exposed groups were small in size, resulting in a limited power to detect an overall increased risk for congenital malformations. For the omeprazole group (n=139), the minimum overall increased risk for RR the study could detect was about 2.5 (1-tailed test). However, since exposure teratogens is likely to result in an increased risk of specific malformations rather than an overall increase in all malformations, this study probably lacked adequate power to rule out a 4-fold increase in risk for specific malformations whose prevalence is about 1 per 1000 or less (e.g., some specific heart defects). The limited sample size did no allow evaluation of potential confounders such as maternal age, family history of congenital anomalies, and use of multivitamins.

## 4. Källén B. Use of Omeprazole during pregnancy – no hazards demonstrable.

1.1. Summary

This retrospective cohort study is an extension of an earlier study based on the Swedish Medical Birth Registry (Källén B, 1998). The study population was expanded to include infants born between 1997-1999 to the cohort of infants born between 1995 and early 1997. This study also excluded pregnancies that resulted in spontaneous abortions and pregnancies that were terminated as a result of a prenatal diagnosis of a congenital malformation. A total of 955 infants exposed to Omeprazole were identified: 863 exposed in early pregnancy, and 131 later in pregnancy. Those exposed in early pregnancy included some exposed later in pregnancy, and vice versa. Outcomes studied include: congenital malformations, perinatal survival, low birth weight, and low Apgar scores, and hospitalization through 1997.

The rate of twinning was slightly lower among infants with earlier exposures compared to infants in the general population (2.3% vs. 3.1%). Similarly, the rate of malformations was slightly lower among infants with earlier exposures compared to infants in the general population (2.5% vs. 3.6%). Infants with earlier exposures had rates of perinatal mortality and low birth weight that were similar to infants in the general population, but the number of infants with these outcomes was small. This study identified 5 additional cases of malformations from the Medical Birth Registry among infants born in the period of extension (1997-1999). The odds ratio for having a malformed infant, stratified for year of birth, maternal age, parity, and maternal smoking was 0.82 (95% CI 0.50-1.34). There were eight infants with cardiac defects, seven of which were considered to be mild. The stratified odds ratio for any cardiovascular malformation was 1.9 (95% CI 0.8-4.4), and for VSD 1.7 (95% CI 0.5-3.9).

There was no evidence of an increased risk of low Apgar scores or of hospitalizations by the end of 1997 among infants who had been exposed to Omeprazole in pregnancy.

1.1. Strengths and limitations

4.2.1. Strengths

This study has the same strengths as the earlier study and, in addition, has the strength of including 371 (863-492) additional infants exposed early in pregnancies.

4.2.2. Limitations

This study has the same limitations as the earlier study: possible selection due to exclusion of spontaneous abortions and pregnancies terminated due to a prenatally detected malformations; and underascertainment and misclassification of cases after birth. The slightly lower rate of malformations among the exposed early in pregnancy compared to the rate in the general population would suggest that prenatal detection and pregnancy termination may have it made difficult, if not impossible, to see an excess risk from Omeprazole. The report does not make clear what proportion of the pregnancies classified as early exposures had late exposures and vice versa. Without a better clarification of the classification of exposure, more information on the rates of spontaneous abortions on the exposed and unexposed, the rates of pregnancy terminations in the exposed and unexposed, and some data on the frequency distribution of malformations in the exposed and unexposed, studies based on the Swedish Birth Register are not likely to provide a reliable answer to the question of whether Omeprazole is safe to use early in pregnancy. This study had limited power to rule moderate adverse effects on pregnancy outcomes from exposure to Omeprazole later in pregnancy.

**5. Synthesis**

These retrospective cohort studies provide no evidence for an increased risk of congenital malformations or other pregnancy outcomes in relation to omeprazole use during the first trimester of pregnancy. However, findings from these studies are difficult to interpret in light of several methodological issues, including: potential selection bias related to the exclusion of spontaneous abortions and pregnancy terminations due to prenatal diagnoses of congenital malformations; limitations in case definition, ascertainment, validation, and classification; potential confounding; and inadequate power to detect increased risks for specific malformations (e.g., cardiac septal defects) or other specific pregnancy outcomes.

Adolfo Correa, MD, PhD
Acting Chief, Surveillance and Epidemiology Section

Birth Defects and Pediatric Genetics Branch
Division of Birth Defects, Child Development, and
Disability and Health
National Center for Environmental Health
Centers for Disease Control and Prevention

9.05.00

**Comments on the design characteristics and feasibility of a large, prospectively designed epidemiological study of women exposed to Omeprazole during pregnancy**

Since some of the issues of concern regarding use of Omeprazole during pregnancy relate to spontaneous abortion and congenital heart defects among offspring, desirable design characteristics of a prospective cohort study to address these issues include:

- Determination of the minimum excess risk that would be of clinical and public health importance to detect.

- Estimation of early pregnancy losses.

- Estimation of size of cohort study to detect the minimum excess risk for spontaneous abortions, and for malformations accounting for early pregnancy losses. The following numbers provide a rough idea of the kind of sample sizes needed per cohort of exposed and unexposed pregnancies to detect a minimum relative risk for one of the more common major congenital heart defects (i.e., ventricular septal defects) with a baseline prevalence of about 1 per 1000:

| Minimum RR | N per exposure group |
|---|---|
| 2 | 4300 |
| 3 | 1500 |
| 4 | 800 |
| 5 | 560 |

For other heart defects, with a much lower prevalence, the sample sizes would have to be much greater.

- Enrollment of a large cohort of women planning a pregnancy or who have just become pregnant.

- A substantial number of such women end up using Omeprazole during the first trimester of pregnancy.

- Baseline and regularly scheduled interviews and examinations of all women in the cohort are conducted to ascertain

    - Pregnancy status
    - Use of Omeprazole
    - Use of other prescription and nonprescription drugs
    - Use of alcohol and cigarette smoking

- Use of vitamin supplements
- Illnesses during the first trimester

- Follow-up of all women to ascertain, evaluate, and validate all pregnancy outcomes, using standardized procedures.

- Create and manage, on an ongoing basis, a complex database.

- Conduct timely evaluations of safety issues.

However, implementation of such a prospective cohort study of pregnant women exposed to Omeprazole, or to any other single drug, is likely to require extensive resources and be prohibitively costly and inefficient. An alternative and probably more efficient approach would be to develop and implement a protocol for post-marketing surveillance for a variety of drugs, prescription and nonprescription, using standardized methods and applying this to a large population base over an extended period of time. The infrastructure for this type of surveillance might be a network of centers likely to serve as a resource for information or prenatal care to large populations of women of reproductive age (e.g., major medical centers, HMOs). Such a post-marketing surveillance network would be able to develop and use standardized procedures to collect baseline and follow-up information on all participants, including information on drug exposure, and schedule follow-up contacts of participating women with obstetricians, pediatricians, and dysmorphologists and other specialists (e.g., clinical geneticists, pediatric cardiologists) at regular intervals, around the delivery dates, and during infancy. This monitoring system would also be able to carry out follow-up contacts at one year of age and to request medical records as needed. A data coordinating center for the network could be set up to collect and process the data, to implement quality assurance and control procedures, and to effectively manage such a complex database. Such a data coordinating center could be structure to conduct timely evaluations of trends of drug use among pregnant women, of safety questions about specific drugs or combinations of drugs in comparison to exposures that are less likely to have adverse effects on pregnancy outcome, and to conduct regular screening for potential adverse effects through nested case-control studies and case-crossover studies.

The above alternative approach will require extensive resources. It might be useful to come up with budget estimates for such a monitoring system, compare such budget estimates with the current total budget for all existing pregnancy drug registries, and evaluate the added value for the extra cost.

Adolfo Correa, MD, PhD
09.05.00

**Review of twenty adverse event reports in relation to exposure to Omeprazole**

The twenty adverse event reports include:

18 reports of congenital birth defects or chromosomal disorders
1 report of a fetal death, and
1 report of hypoglycemia, respiratory distress and pneumonia.

Imputing any kind of probability of association of these reports to exposure to Omeprazole is subject to a great deal of uncertainty for several reasons. These reports come from different parts of the world over a period of several years and without sufficient information to assess the completeness and accuracy of such reports. The population at risk that gave rise to these cases is an ill-defined universe. Consequently, there is no way of estimating the rate of adverse events among exposed and unexposed pregnancies, and of determining the adverse events among exposed pregnancies represent more than the expected number of events.

Nonetheless, based on the limited information available in these reports, I classified the cases of birth defects into one of the following categories of association with in utero exposure to Omeprazole - possible, unlikely, and unclear, using the following two criteria of temporal relation and alternative explanation:

Possible: if there was an indication that exposure to Omeprazole might have occurred during the first trimester of pregnancy.

Unlikely: if there was little indication of exposure to Omeprazole during the first trimester of pregnancy or if there was a strong alternative explanation for the defect, such as a chromosomal disorder or recognizable syndrome.

Unclear: if time of exposure during pregnancy was not specified.

I did not consider probable as a classification category because I am not aware of any studies in animals or humans suggesting that exposure to Omeprazole during the period of organogenesis may be associated with birth defects.

Of the eighteen reports of birth defects, I classified sixteen as possible, two as unlikely, and one as unclear. See attached table. Among the sixteen reports of birth defects classified as possible, there were four reports indicating the presence of risk factors for birth defects, including maternal diabetes, febrile illness, and family history of birth defects. Since the etiology of birth defects is thought to be multifactorial, these risk factors could also be considered as alternative explanations for the observed defects. It is also possible that the presence of such risk factors might have enhanced the susceptibility to teratogenesis by Omeprazole.

To be consistent, I am inclined to classify the reports of fetal death and of hypoglycemia, respiratory distress and pneumonia as possible. However, without more information about the pregnancies, it is difficult to be sure that there were no better explanations for these events. In the case of hypoglycemia with respiratory distress and pneumonia, based on the information available, it is difficult to know the actual sequence of events and, therefore, to identify the most likely cause. If one could be sure that pneumonia had occurred first, one might just as easily postulate that infection was the underlying cause of respiratory distress and stress-induced hypoglycemia, without needing to invoke any etiologic role for Omeprazole.

Adolfo Correa, MD, PhD
09.06.00

| No. | REPORT # | REACTIONS | OMEPRAZ | OTHER | F HX | M AGE | OTHER | CLASS |
|---|---|---|---|---|---|---|---|---|
| 1 | | Strabismus, Duane | 9 days, 1st mo prg | carbenoxolone | neg | 25 | | Possible |
| 2 | | hydrancephaly, clubfeet | 3.2 mo, 20 mg | insulin | ? | 28 | DDM | Possible |
| 3 | | meningomyelocele, cl+p | entire prg, 40 mg | antibiotic for cough | neg | 28 | | Possible |
| 4 | | bculo-auricular-fronto-ns | at pregnancy dx | ranitidine, 2nd | ? | 39 | gastric ulcer | Unlikely |
| 5 | | VSD | 1st month | promethazine, ran+ | | 34 | febrile viral | Possible |
| | | anencephaly | 1st trimester | | ntd | 31 | | Possible |
| | | anencephaly (prenatal) | 6-13 weeks gestat | | | 20 | | Unlikely |
| 6 | | cleft palate | time of use unspec. | gaviscon, ponstan | | 30 | | Unclear |
| 9 | | pyloric stenosis | 3rd trimester | ranitidine, 3rd, 16 d | | 33 | | Possible |
| 10 | | facial deformity | 1, 2, 3 trimesters | ranitidine | | 39 | | Possible |
| 11 | | maxillary fibrous dysplas | 1st trimester | | | ? | | Possible |
| 12 | | fetal death | 1st trimester | amoxicillin, flagyl | | ? | | No defect |
| 13 | | chromosomal rearranget | 1st trimester, durtn? | zantac | | ? | | Unlikely |
| 14 | | anophthalmia, hydrops f | 1, 2, 3 trimesters | ? | | 34 | duod ulcer | Possible |
| 15 | | hypoglyc/resp dist/pneu | 3rd trimester | amoxic, mag sulfat | ? | 34 | htn/gluint/pud | No defect |
| 16 | | hypoplastic left heart | 1st trimester | h2 antag, kflx, caraf | ? | 21 | gu an/hx uti | Possible |
| 17 | | anencephaly | 1st trimester | prenatal vitamins | ? | ? | hiatal hernia | Possible |
| 18 | | limb deform, l lower arm | 1st trimester | ranitidine | ? | 27 | gastritis | Possible |
| 19 | | severe talipes | 1, 2, 3 trimesters | folic acid, vitamins | ntd | 37 | ge reflux | Possible |
| 20 | | anencephaly | 1, 2, 3 trimesters | GIFT (ART) | talipes | 36 | ge reflux | Possible |

RFC-822-headers:
Received: from cdswss1.cder.fda.gov
("port 4110"@cdswss1.cder.fda.gov [150.148.150.21])
by mail.cder.fda.gov (PMDF V6.0-24 #42130)
with ESMTP id <01JTUUSSZBW690MVHH@mail.cder.fda.gov>; Wed,
06 Sep 2000 14:57:35 -0400 (EDT)
Received: from 198.246.96.75 by cdswss1.cder.fda.gov with SMTP
( WorldSecure Server SMTP Relay(WSS) v4.3); Wed, 06 Sep 2000 14:55:32 -0400
Received: from mcdc-us-smtp4.cdc.gov ([198.246.96.75])
by ocswall4 via smtpd (for cdswss1.cder.fda.gov [150.148.150.21])
with SMTP; Wed, 06 Sep 2000 18:52:49 +0000 (UT)
Received: from 198.246.96.17 by mcdc-us-smtp4.cdc.gov
(InterScan E-Mail VirusWall NT); Wed,
06 Sep 2000 14:56:36 -0400 (Eastern Daylight Time)
Received: by mcdc-us-imsgate.cdc.gov with Internet Mail Service ( 5.5.2651.58)
id <SMSBCMW6>; Wed, 06 Sep 2000 14:56:41 -0400
X-Mailer: Internet Mail Service (5.5.2651.58)
X-Server-Uuid: 00796fd4-893e-11d3-8ed3-0008c75df4f2
X-WSS-ID: 15A84CA9750255-01-01

Printed by Maria Walsh

# Electronic Mail Message

S vity: COMPANY CONFIDENTIAL

**Date:** 05-Oct-1999 04:10pm
**From:** Mary Dempsey
DEMPSEYM
**Dept:** HFD-440 PKLN 15B18
**Tel No:** 301-827-3176 FAX 301-480-0628

**TO:** See Below
**Subject:** Omeprazole Consult request RE: pregnancy category

Maria,

Due to the short review time, three different Epi reviewers worked on the completion of your consult request.

The United Kingdom and Italy Epi Study was reviewed by David Graham.

The Swedish Epi Study was reviewed by Diane Wysowski.

The Canadian Epi Study was reviewed by Judy Staffa.

Please see the attachment that contains the comments of each reviewer.

We hope that our reviews will assist you with your action letter.

Thanks,
MaryD

D: hution:

T: aria Walsh ( WALSH )

CC: Evelyn Rodriguez ( RODRIGUEZE )
CC: Toni Piazza-Hepp ( PIAZZAHEPPT )
CC: David J. Graham [HFD-733 EPI] ( GRAHAMD )
CC: Judy Staffa ( STAFFAJ )
CC: Diane Wysowski ( WYSOWSKI )
CC: Mary Dempsey ( DEMPSEYM )
CC: Lilia Talarico ( TALARICO )

10-6-99
* Please review prior to our meeting at 1pm (Rm 13B-45)
Maria

David Graham's comments on manuscript "Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcome" by Ruigomez, Garcia Rodriguez, Cattaruzzi, etal.

1. No definition was provided of the definition of the duration or timing of first trimester for purposes of exposure classification.

2. No breakdown of timing of exposure within the first trimester was provided.

3. Spontaneous abortions and ectopic pregnancies were excluded.

4. In the UK, outcome was based on diagnosis codes in the computerized record and do not appear to have been validated.

5. The exposed cohorts were small: 237 cimetidine, 139 omeprazole, 330 ranitidine, 1575 non-exposed.

6. Data on malformations are not presented separately for the UK and Italian cohorts in Table 2, precluding closer examination of the data.

7. Although not cited by the authors, I noted 2 cases of cardiac septal defects in the omeprazole cohort compared with 3 in the non-exposed cohort, yielding a relative risk (RR) of 7.6 (95% confidence interval 1.3-44.8), p=.0555 Fishers exact. Also, there were 2 cases of hypospadias in the cimetidine cohort compared with 1 in the non-exposed (RR 13.1 (1.2-144.8) p=.048 Fishers exact).

Brief Discussion

This study is extremely underpowered to exclude the possibility of large increases in relative risk for selected major malformations. The study focused on looking for an increase in the overall rate of <u>all</u> defects. This is not a realistic way to evaluate a drug for potential teratogenicity because human teratogens do not cause an increase in <u>all</u> defects. Rather, teratogens generally act upon a specific embryologic target that represents the anlage of a specific tissue type. It is for this reason, that specific teratogens are generally associated with specific types of malformations.

With this background, it is no surprise that this study did not detect an increase in risk of <u>all</u> defects. More importantly, with an exposure cohort of at most 139 for omeprazole, there was virtually no power to exclude statistically significant and clinically meaningful increases in "common" specific malformations such as spina bifida (background rate: 1 per 2000 live births).

While the authors stated that there were no increases in the occurrence of specific malformations, we found evidence suggesting a possible increase in cardiac septal defects with omeprazole (at least 1 of 2 was a venticular-septal defect: mother's id 1127, pg 8-001-174), and hypospadias with cimetidine. In the context of this review, these observations should not be interpreted as definitive proof of association, but they should probably be examined further.

Conclusion

Contrary to the authors' conclusions, this study should not be interpreted as demonstrating that omeprazole is free of teratogenic risk. The finding of no increase in risk for all malformations is not equivalent to a lack of teratogenic risk. The current study was severely underpowered for purposes of detecting important increases in risk of virtually any specific major malformation. Further evaluation of the observations regarding cardiac (especially venticular) septal defects with omeprazole, and possibly hypospadias with cimetidine, should be considered.

## Comments by Epi reviewer Judy Staffa

As requested, I am providing comments from my review of the Motherisk study "A Preliminary Report on the Safety of Omeprazole during Pregnancy". Because of the short timeframe allowed for the review, my comments will be brief and focus only on the issues I believe to be most important.

1. I believe that this study is well-done by researchers using a well-established data source of women who have contacted a teratogen information center after using a drug during pregnancy. These women are then enrolled to prospectively study the outcome of their pregnancy. The study combined populations from several centers (Toronto, Rome, Milan and Lyon), and although the investigators report that the study populations from each center were the same, it would be more reassuring to see the comparative data and to know that the methodologies in each center were similar.

2. Because of the prospective nature of the follow up of women, it was possible for the investigators to look at spontaneous abortions as an outcome, which is a difficult outcome to study. I believe this outcome was important for omeprazole in particular because the investigators stated that "a slight increase in fetal loss was noted after using the highest doses" during the animal studies. To my knowledge, this is the only outcome with any "a priori" hypothesis of association with omeprazole, and therefore crucial to study.

Initially, there appeared to be a non-statistically significant difference in frequency of spontaneous abortion between the omeprazole group (14%) and the other 2 comparator groups (8% each). However, 2 cases in the omeprazole group had scleroderma and 1 case took cytotoxic drugs during the first trimester. After excluding these cases, the frequency in the omeprazole group drops to 11.5%. Therefore, it does not appear to be occurring at a significantly higher rate in the omeprazole group, which is somewhat reassuring.

3. Although the numbers of exposed pregnancies in this study were not large (n=113 in each group), it does not appear to provide any evidence suggesting that omeprazole is frequently associated with the combined group of major birth defects. However, since major birth defects occur rather rarely, one would need much larger studies to examine each specific defect individually. If there were a hypothesis suggesting a mechanism for omeprazole to cause a specific birth defect (such as case reports or animal data), then one could focus in on such an outcome with a case-control study, since omeprazole is quite widely used. I am unaware at this time of such a hypothesis.

4. There was only one case of ventricular septal defect in the omeprazole group in the Motherisk study, but several occurred in the omeprazole-exposed groups in the Swedish study and the GPRD/Italian study. I am unsure of the background incidence of this type of defect since it seems to be a relatively common type of congenital heart defect; with more time, I would investigate this more thoroughly. With the relatively small numbers of pregnancies studied, it is impossible to determine if the observed frequency of this outcome is simply reflective of the background rate or something to be concerned about. It is of note, however, that in the Swedish study none of the VSD cases were referred to a Child Cardiology Center, suggesting that perhaps the severity of the cases was low. It might be useful to follow up with the investigators of these 3 studies to get more information about the cases of VSD.

..EMORANDUM

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

DATE: October 5, 1999

FROM: Diane K. Wysowski, Ph.D., Epidemiologist,
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Evelyn Rodriguez, M.D., M.P.H., Director,
Division of Drug Risk Evaluation II, HFD-440

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

**SUBJECT: Evaluation of a Study of the Risks of Congenital Malformations in Association with Use of Acid-Suppressing Drugs in the First Trimester**

PID # 99337

The following is a critique of the study entitled "Delivery outcome after the use of acid-suppressing drugs in ly pregnancy with special reference to omeprazole."

The major concern of this study is the number of individuals exposed to omeprazole and the H2 receptor antagonists in the first trimester of pregnancy during the study period. The sample size is such that the investigators are only able to exclude the drugs as important causes of major malformations.

2.As is typical for these types of studies, the data do not include outcomes of induced abortions and spontaneous abortions. It would be useful to know what proportion of women who reported for the first prenatal visit and took proton pump inhibitors and H2 receptor antagonists subsequently had induced and spontaneous abortions. These proportions could then be compared with national data stratified by age, parity, and smoking history to determine if there were higher frequencies of induced and spontaneous abortions in the group who used acid-suppressing drugs.

3.It might be useful to have data on frequency of use of the acid reducers as these drugs may be taken sporadically, or on a regular basis, for heartburn/reflux.

4.In the United States, some of the acid-reducing drugs are available over the counter. The investigators should comment on whether acid-reducing drugs are available only by prescription in Sweden. If available over the counter, the investigators should comment on whether use of OTC drugs was requested in the interview.

5.The authors should present data on loss to follow-up from the time of first prenatal visit to outcome of delivery.

6.The authors should collect information on use of multivitamins around the time of conception and in the st trimester and they should consider stratifying on this variable.

7.It would be useful to have a control group of individuals who had gastritis and who did not use either a proton pump inhibitor or an H2 receptor antagonist during early pregnancy.

Despite these concerns, I believe the investigators should be commended for their systematic study of the teratogenic effect of drugs. Their approach improves upon passive surveillance, case reports, and animal research that are so often relied upon for evaluation of teratogenicity risk.

Diane K. Wysowski, Ph.D.

# Memorandum of Consultation

Date: September 21, 1999

From: Sandra L. Kweder, M.D.
Director (Acting)
Office of Drug Evaluation IV (HFD-104)
Co-Chair, FDA Pregnancy Labeling Taskforce

To: Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Hematologic Drug Products (HFD-180)

Subject: NDA 19-810 S-058
Omeprazole label: Pregnancy subsection

Consultation Request Date: 8/25/99
Requested Completion Date: 9/22/99

Original Consultation Request

*"In light of ongoing deliberations by the Pregnancy Labeling Task Force regarding the requirements for Pregnancy Category, we are requesting your assistance in answering the following questions: Are the human data contained in this supplement sufficient for labeling this drug as Pregnancy Category B? If not, what kinds of human data are needed to support a change in the Pregnancy Category from C to B? Are the sponsor's proposed revisions adding the results of the epidemiological studies adequate? What additional Pregnancy Category issues should we address?*

*"Please be aware that the sponsor is developing this drug for the OTC treatment of heartburn and plans to submit the NDA in February 2000. The NDA will be discussed at a Joint Advisory Committee mostly for safety issues one of which is that the prescription drug is labeled Pregnancy Category C."*

Material Submitted in Consultation

1. Copies of email notes from Maria Walsh to Sandra L. Kweder, M.D. (2/2/99) and response (2/8/99).
2. Astra Pharmaceuticals cover letter to NDA 19-810 (SE8-058), dated 10/7/98, accompanied by proposed label changes.
3. Medical Officer Review of submitted data, dated 1/21/99.
4. Pharmacologist's Review of submitted data, dated 8/11/99.

Recommendations

1. It is essential that the pharm/tox data and the conclusions that can be drawn from them be stated clearly. From my reading of the review included in this consult packet, I find the preclinical data generally supportive of Category B designation on their own. I strongly recommend that Dr. Joseph DeGeorge, Associate Director of Pharmacology/Toxicology, Office of Review Management, be briefed on this drug and the issues presented by the new data.

2. The human data submitted might be adequate to support a change in category. The sponsor should be asked to consider obtaining original data and more detail from the provided studies, particularly the Motherisk study. If this can be done, then CDER's epidemiology experts should review these and assist in providing confidence intervals around the results. In the absence of doing so, it might be more useful to simply be able to state in the label from these studies what magnitude of risk for endpoints of interest can and can't be ruled out.

3. Regardless of whether the Pregnancy Category is changed information from the human studies should be summarized in the label to assist clinicians making therapeutic decisions about omeprazole for pregnant women. More importantly, the types of findings in the animal and human studies reported in this NDA make it essential that the information be clearly presented in a way that does not incite alarm in patients (or clinicians) faced with inadvertent exposure in pregnancy (i.e., when a woman has been taking omeprazole for some period of time prior to knowledge of her pregnancy).

4. Regardless of the Division's final decision about whether to grant the sponsor's request for a change to Category B from C, the sponsor should institute a pregnancy registry for this drug. I expect that with appropriate recruiting efforts it will not be difficult to enroll. A component of the registry that employs long term follow-up of children exposed for some minimum duration in utero should be instituted as well, based on carcinogenicity data.

I. Consultation Background

The NDA supplement submitted by Astra for the change of the Pregnancy subsection of labeling from Category C to Category B is proposed on the basis of several sources of information. First, the sponsor has submitted additional data to the preclinical toxicology database, predominantly from studies that predate the original NDA submission, but which were conducted in Japan and not previously translated into English. Second, the sponsor has provided information from three epidemiology studies in humans in support of the lack of any associated teratogenicity or adverse fetal effects of omeprazole when taken by pregnant women. Findings from these preclinical and clinical data sources are reviewed in the Pharmacology/Toxicology review and the Medical Officer review and will not be described in detail here. I will address the regulatory framework in which the issues arise for this

NDA; provide some general comment on the preclinical and epidemiology data and what it is reasonable to expect, and; provide recommendations.

II. Regulatory Framework: Pregnancy Categories

The regulations governing how to label drugs for use in pregnancy reside under CFR 201.57 (f) (6). Requirements set forth in this regulation for Pregnancy category B and C are as follows:

> ***Pregnancy Category B.*** If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the label shall state: "Pregnancy Category B....." If animal reproductive studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B....." The labeling shall also contain a description of the human studies and a description of the available data on the effect of the drug on the later growth, development and functional maturation of the child.
>
> ***Pregnancy Category C.*** If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risk, the labeling shall state: "Pregnancy Category C...." If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C..." The labeling shall contain a description of any available data on the growth, development, and functional maturation of the child.

For practical purposes, the distinctions between categories C and B lie in two areas. The first is how worrisome the animal data are. Animal data that show no adverse effect or an effect which, in the judgement of the pharmacology/toxicology (pharm/tox) reviewer, is of minimal concern, have historically been considered to warrant assignment of Category B. An example might be when an effect on the fetus is seen that is considered to be directly related to maternal impairment or toxicity (e.g., the dam in animal studies at high doses often displays general signs of toxicity from the drug administered, leading to poor weight gain with secondary effects on the fetus). Animal data that clearly indicate an effect on the fetus that can not be attributed to maternal toxicity, but point directly to the drug itself being the culprit are assigned Category C. Unfortunately, many drugs lie in an ill-defined area of uncertainty that make it unclear whether they warrant a B or a C designation. In such cases, the predictive value of the animal species in which the finding occurs, the relevance of the finding to humans and the pharmacology of the drug must be taken into account in deciding which category to assign.

The second area of distinction relates to how much clinical data are available. While the CFR indicates that data from adequate and well-controlled studies are required, it does not

A. *United Kingdom and Italy Epidemiology Study: Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes.*

This study was conducted using the U.K. General Practice Research Database (GPRD) and a birth registry and prescription database from a region in northern Italy. The GPRD is one of the most complete clinical practice/research databases in the world and is highly sought after for studying drug safety issues. It has been used for studies of pregnancy outcomes in the past. It has a long record of validated data and methods. Less is known about the Italian registry and prescription database. Both data sources included a control group of unexposed women. Endpoints assessed were structural malformations detectable at birth (whether live or stillbirth) and out to one year. There were 5 reports (among 134 omeprazole exposed mother-infant pairs) of congenital anomalies. These were tongue tie (1); cardiac septal defect (2); dysplastic hip/click (1); inguinal hernia (1). There was no significant difference in pattern or in rates of findings between omeprazole-exposed patients and controls.

Strengths of the study:

- The GPRD is a well known and potentially powerful database that is considered reliable for conducting epidemiology studies of drug safety, including those addressing pregnancy outcomes.
- Non-exposed controls were included for both the U.K. and Italy site.
- Endpoints could be reported as late as one year after birth.

Weaknesses of the study:

- The numbers of patients exposed to omeprazole is very small (97 in GPRD; 37 in Italy).
- Spontaneous abortions were not included in the study, an endpoint that would be of interest based on animal data.
- It is impossible to tell from the data how many women received combinations of omeprazole and an H2-blocker.
- The results of the study do not clearly distinguish exposures by timing in pregnancy, although the methods of the study indicate that doing so is potentially possible. However, the number of events is so small and types of events are quite variable, making this less of an issue for this study.

Consultant's Comment: As described by the medical officer who reviewed the study, it appears that with the small number of exposures and events in this study only a large risk of anatomic malformations can be ruled out, i.e., the risk is not likely to be greater than 7 per 1,000 exposures. This is not much different than the background rate of congenital anomalies in western countries, generally estimated at 4-6 per 1,000 live births.

B. *Swedish Epidemiology Study: Delivery outcomes after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole.*

This retrospective cohort study was conducted through the Swedish Medical Birth Registry over a two year period. Congenital malformations and various standard measures of fetal growth and development were extracted from the records linked to this database. Omeprazole exposure was reported for 262 women of 200,000 births. The control group was non-exposed mothers from the same database. There were some differences between the exposed and non-exposed cohorts (the former had an increased use of concomitant medications; were older and tended to smoke more). Eight abnormalities were reported among the 262 omeprazole mother-infant pair. These included: ventricular septal defect (3); patent ductus arteriosus (1); unspecified cardiac defect (1); urethral valve (1); facial anomaly (1); Down Syndrome (1). Overall, the numbers and rates of events was not significantly different for the omeprazole group compared to controls or other acid suppressant exposed groups.

Strengths of the study:

- This national registry has been in existence for many years and is not likely to be subject to systematic bias.
- An attempt was made to capture and analyze women who were exposed to more than one acid-suppressing drug.

Weaknesses of the study:

- No doses or duration of exposures to omeprazole were reported.
- Once again, rates of spontaneous abortions were not assessed.
- The rates of events only address combined malformation rates. No attempt is made to quantify rates of individual system malformations, for example. This is often a futile exercise when overall event rates are small. However, it is interesting in this study that half of the anomalous findings in the omeprazole group were cardiac structural abnormalities.

Consultant's Comments: Once again, the event rate in this study was not large. The findings of cardiac structural abnormalities in the omeprazole exposed group is unlikely to be significant, but should be addressed.

C. *Motherisk Epidemiology Study: A preliminary report on the safety of omeprazole during pregnancy.*

Motherisk is the oldest and most sought after teratogen information service in the world. Patients who call the service for information are offered enrollment into cohort studies. This study included all calls for omeprazole exposure to Motherisk since its inception and calls to several similar systems in Europe. The authors report on 113 omeprazole exposures (59 from Toronto), with over a third also taking other antacid medications or pro-kinetics. Most exposures (nearly 90%) were in the first trimester. Overall malformation rates were similar for omeprazole treatment groups and disease-paired controls. There was a numerically higher rate of spontaneous

abortions in the omeprazole group (14%), versus 8% in the disease-paired controls and 8% in the non-teratogen treated group, which was not statistically significant.

Strengths of the study:

- As indicated, the Motherisk group has a long history of conducting such studies.
- Spontaneous abortions were assessed.
- Most exposures were identified as first trimester. This is still not detailed as one would like, but in epidemiology studies, is a step in the right direction.

Weaknesses of the study:

- The pooled nature of the data across several different systems is concerning without reassurance that collection and follow-up methods were indeed identical.
- Once again, overall, the numbers of exposures are small, making any differences between treatment groups and outcomes, other than those that are dramatic, unlikely to be detected.

Consultant's Comments: In general, this data source has the potential to offer more detailed information. Motherisk maintains very detailed records of its enrollees, and some of the questions about dosing and exposure raised by the medical officer's review might be able to be addressed by the investigators, particularly at the Toronto site.

D. *Spontaneous Reporting System and Other Sources*

The medical literature does not offer much additional information to what is described, above. The sponsor's reports of the findings from spontaneous reports also are not especially helpful (3 cases of general heart defects and 4 cases of anencephaly and other assorted findings).

V. General Comments

1. Overall, the studies presented, while limited, do not raise strong concerns about omeprazole being a drug that has a substantial risk of inducing congenital malformations when taken in pregnancy. In addition, the preclinical data available do not suggest a risk of specific congenital malformations. Certainly a small risk can not be excluded from these data, but a high risk seems unlikely.

2. The data do not address the risk of embryolethality, with the exception of the study by the Motherisk group that, with small numbers of exposures, concluded there was no statistically significant increase in the rate of spontaneous abortion. This is an extremely difficult endpoint to study in any of the settings employed in these studies, as many spontaneous abortions will occur prior to knowledge of the woman that she is pregnant or even seeks testing for pregnancy.

3. Certainly the studies described do not constitute the type of data that one normally expects to see in controlled clinical trials of a new drug. From that standpoint it is

tempting to conclude that they are not "adequate and well controlled trials." On the other hand, the regulatory definition of adequate and well controlled is, in fact, quite broad, leaving substantial discretion to the FDA in this regard. When appropriate, historical controls or epidemiology data can be considered to meet the standard, as this is sometimes all that is available.

4. Given the above, it seems reasonable to expect that sound epidemiology studies could fit the bill of adequate and well controlled studies for purposes of assessing safety in pregnancy. This is particularly the case as the likelihood of enrolling and completing a randomized controlled trial of a drug to treat an indication that is not specific to pregnancy in pregnant women, with a size that has adequate power to detect differences in pregnancy outcomes of interest, is remote. The barriers to such a study are overwhelming, from simple numbers of available patients to IRB and legal issues. While many believe such studies are ethical and reasonable, the only disease in which studies like this have been successfully completed is hypertension – and only once to my knowledge, /

5. The studies reported by the sponsor do have limitations. However, it may be possible to put confidence intervals around the differences detected between treatments and controls. It may also be possible to obtain additional information about the data itself, such as information on timing of exposure, etc., before reaching final conclusions. I suggest that the Motherisk data would be the most fruitful for this purpose. Doing so would likely require a major clinical amendment to the NDA or, more likely a new submission if it is ultimately deemed necessary to have.

6. An additional study that could be undertaken by the sponsor, particularly if their interest is in obtaining an OTC indication, is a rigorous pregnancy registry. CDER has recently issued a Draft Guidance Document for Industry on Establishing Pregnancy Registries that could provide the sponsor with some basic information on where to begin their planning. Certainly such a registry should be required for the product if it is given OTC status, as exposures will likely increase and the need to have more detailed information will be important. Whether it should be required prior to OTC switch is a review issue that I suggest would be appropriate for an advisory committee to address.

7. It is of note that dosing in pregnancy is not addressed in any of the materials I have available for review. If a drug is expected to be used widely by pregnant women, it would seem reasonable that the sponsor would conduct some studies assessing its pharmacokinetics and tolerance in pregnancy. Or, in the absence of such formal studies, an attempt could be made to extrapolate animal PK data from pregnant and nonpregnant dams to humans, with subsequent confirmation in at least a few patients taking the drug for appropriate therapeutic indications during pregnancy.

8. It is also of note that the carcinogenicity concerns raised for omeprazole have not been addressed by the sponsor in terms of their relevance to exposure in utero. This may already have been discussed by HFD-180 in previous reviews.

9. As a general comment, it is not essential that a product carry a Pregnancy Category designation of B or A in order to obtain OTC status. A recent case in point are nicotine replacement products which are Categories C and D, to say nothing of alcohol or cigarettes which would likely carry Category D (or X) designation if they were drugs under FDA jurisdiction.

10. Overall, I agree that the findings of the data in this package suggest that there should not be great worry associated with the use of omeprazole in pregnancy, at least in the short term. Whether the drug is a Category B or a Category C is less important than describing the data that exist well to facilitate clinical decision making.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# REQUEST FOR CONSULTATION

TO *(Division/Office)*: Pregnancy Labeling Team
Attention: Sandy Kweder, M.D., WOC2, Room 6069

FROM: The Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Maria Walsh, PM, Pkln. Bldg., Room 6B-17

| DATE: 10/8/02 | IND NO. | NDA NO. 19-810/SE8-058 | TYPE OF DOCUMENT Supplement labeling | DATE OF DOCUMENT 8/16/02 |
|---|---|---|---|---|
| NAME OF DRUG Prilosec (omeprazole) Delayed-Release Capsules | PRIORITY CONSIDERATION | | CLASSIFICATION OF DRUG 1S | DESIRED COMPLETION DATE **11/12/02** |

NAME OF FIRM: AstraZeneca LP

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

**II. BIOMETRICS**

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is a follow-up consult to our original consult on 8/25/99 (please see attached consult review by Dr. Kweder dated 9/23/99). This is the fourth review cycle for N19-810/SE8-058, Prilosec (omeprazole) which provides for revision of the PRECAUTIONS section of the package insert to add preclinical information and clinical information from three epidemiological studies in pregnant women. The Division has decided to retain the Pregnancy Category C.**

**The attached labeling has been accepted by the sponsor ✓ ✓ ✓ ✓ (shown as strike-out on page 20), which is the issue for this fourth review cycle. Before we approve the supplement (due date 2/3/03), we are requesting that you please review the attached labeling under PRECAUTIONS, Pregnancy for final acceptability of the language regarding the human data.**

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

Maria Walsh
10/8/02 03:18:27 PM

# MEMORANDUM OF TELECON

DATE: February 12, 2002

APPLICATION NUMBER: NDA 19-810/S-058
Prilosec (omeprazole) Delayed-Release Capsules

BETWEEN:

Name: Gary Horowitz, Ph.D., Executive Director, Regulatory Affairs
Phone: (610) 695-1008
Representing: AstraZeneca LP

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Labeling discussion: Finding of brain astrocytoma in 52-week toxicology study in rats.

BACKGROUND: Supplement 058 was submitted on October 7, 1998 and provides for revisions to the PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility*; *Pregnancy;* and *Nursing Mothers.* These revisions included the addition of information regarding three epidemiological studies on the use of omeprazole during pregnancy and a change in the *Pregnancy Category* from *C* to *B.* This supplement was not approvable on October 7, 1999 and subsequently approvable on February 7, 2001 pending labeling revisions.

The sponsor submitted a complete response to the February 7, 2001 approvable letter on August 16, 2001 with the following proposed revisions to the PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility* section of the package insert.

**PRECAUTIONS**

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs. 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs. 26%) but still

showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. ~~In a 52-~~

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

Dr. Jasti Choudary, Supervisory Pharmacologist, regarding the finding of brain astrocytoma in a 52-week toxicity study in rats in his review dated February 1, 2002. I called Dr. Horowitz on February 7, 2002 and relayed the Agency's recommendation and rationale as outlined in Dr. Choudary's review.

[illegible] respect to spontaneous occurrence of brain astrocytomas in Sprague-Dawley rats. Since the user fee goal date for this application is February 15, 2002, Dr. Horowitz requested that an approvable action be taken on this review cycle allowing the sponsor time to obtain the Japanese data. I responded that an approvable action can be taken and resolution of this issue can be discussed during the next review cycle.

TODAY'S CALL: After conferring with Dr. Choudary, I called Dr. Horowitz and told him that the sponsor should provide age matched data in the same strain of rat in the same testing lab around the time the study was conducted. Dr. Horowitz said he was planning to obtain contemporary data and thanked me for the advice. The call was then concluded.

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

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/s/
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Maria Walsh
2/12/02 03:03:58 PM
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# MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 18, 1998
**Time:** 9:30 a.m. - 10:30 a.m.
**Location:** Conference Room 6B-45, Parklawn Building

**Application:** NDA 19-810/S-058; Prilosec (omeprazole) Delayed-Release Capsules

**Type of Meeting:** 45-day filing/planning meeting

**Meeting Chair:** Lilia Talarico, M.D., Division Director

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

**Attendees:**

Division of Gastrointestinal and Coagulation Drug Products
Lilia Talarico, M.D., Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Kathy Robie-Suh, M.D., Ph.D., Medical Officer
Jasti Choudary, Ph.D., B.V.Sc., Pharmacology Team Leader
Maria R. Walsh, M.S., Regulatory Project Manager

**Background:** Astra Pharmaceuticals, L.P. submitted supplement 058 on October 7, 1998 for proposed revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility; Pregnancy;* and *Nursing Mothers*. These revisions include a change in the *Pregnancy Category* from *C* to *B*. This supplement has been submitted in response to the Agency's concern regarding the Pregnancy Category and the sponsor's development of omeprazole magnesium tablets for over-the-counter (OTC) use. This concern was communicated to the sponsor at the June 2, 1997 pre-IND meeting, the April 29, 1998 meeting to discuss the proposed actual use study design, the October 7, 1998 meeting to discuss safety issues of OTC use, and in several written communications to the sponsor under IND 54,307 (omeprazole magnesium tablets).

**Meeting:**

1. **Administrative:**

   Filing issues: None

   Administrative issues/requests: None

2. **Nonclinical Pharmacology**

   Filing issues: None

Scientific issues/requests:

The supplement contains eight new preclinical studies including Japanese studies conducted between 1988-92. The supplement does not indicate that these studies conform to US/FDA GLP guidelines.

The new preclinical information will not affect the previous animal data contained in the currently approved labeling which indicate that the drug is fetotoxic. Therefore, adequate human data will be needed to change the Pregnancy Category from C to B according to 21 CRF 201.57 (f)(6)(i)(b), *Pregnancy Category B.*

It was noted that a December 19, 1998 review of 23 reports of congenital anomaly for omeprazole by Ray Alderfer, M.D., M.P.H. of the Office of Pharmacovigilance and Epidemiology revealed that reports of anencephaly and other birth defects do not appear to be excessive for omeprazole in the U.S..

**3. Clinical**

Filing issues: After some discussion, it was decided to file the supplement.

Scientific issues/requests:

The supplement contains three epidemiological studies conducted in Sweden, the United Kingdom/Italy, and Canada. The studies are not prospective, randomized studies but rather observational studies. The incidence of congenital abnormalities was recorded but no information is provided regarding the dose, duration, or time of exposure of the drug nor the number of spontaneous abortions that occurred.

The studies do not appear to meet the regulations under 21 CFR 201.57 (f)(6)(i)(b), *Pregnancy Category B,* which, in the presence of animal reproduction studies that have shown an adverse effect, require adequate and well-controlled studies in pregnant women that fail to demonstrate a risk to the fetus during the first trimester of pregnancy. Therefore, the supplement is likely to be not approved.

It was suggested that the sponsor may wish to conduct a prospective population study looking at drug doses and duration.

**4. Goal Dates**

The 10-month goal date is August 6, 1999. The 12-month goal date is October 7, 1999. It was decided that the supplement should be reviewed as soon as possible.

**Conclusion**

NDA 19-810/S-058 will be filed on December 4, 1998.

Minutes Preparer: Maria Walsh 12/2/98

Chair Concurrence: L Talarico 12-2-98

cc: Original NDA 19-810/S-058
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/PM/M.Walsh
HFD-180/H.Gallo-Torres
K.Robie-Suh
J.Choudary
Drafted by: M.Walsh 11/24/98
Initialed by: J.Choudary 11/29/98
K.Robie-Suh 11/30/98
H.Gallo-Torres 11/30/98
L.Talarico 12/1/98
final: M.Walsh 12/2/98
filename: 19810s58811.45-daymins.doc

MEETING MINUTES

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_X___ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19810
S0038505 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-058 and S-003

AstraZeneca LP
Attention: Nicholas J. Troise
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

We acknowledge receipt on December 23, 2003 of your December 22, 2003 resubmission to your new drug application for Prilosec® (omeprazole) Delayed-Release Capsules for S-058 and S-003.

We note that your December 23, 2003 submission provides a response to our action letter for S-058 and S-003.

We consider your submission a complete, class 1 response to our October 3, 2003 action letter for S-058. The user fee goal date is February 23, 2004.

This amendment also constitutes a complete response to our October 3, 2003 action letter for S-003.

If you have any question, call Monika Houstoun, Pharm.D., Regulatory Project Manager, at (301) 827-9333.

Sincerely,

*{See appended electronic signature page}*

Monika Houstoun, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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Monika Houstoun
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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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S003 & S058

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-003 and S-058

AstraZeneca LP
Attention: Barbara J. Blandin
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Blandin:

We acknowledge receipt on April 4, 2003 of your April 3, 2003 resubmission to your supplemental new drug application for Prilosec® (omeprazole) Delayed-Release Capsules.

These resubmissions proposed revisions to the Prilosec package insert under **PRECAUTIONS**, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers.*

We consider this a complete response to our January 31, 2003 action letter.

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

Sincerely,

*{See appended electronic signature page}*

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

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_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19-810
S003 & S058

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-810/S-058
NDA 19-810/S-003

**DISCIPLINE REVIEW LETTER**

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs
725 Chesterbrook Blvd.
Mailstop: E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your October 7, 1998 supplemental new drug application (S-058) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplemental new drug application proposes revisions to the package insert under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, and Nursing Mothers.**

We also refer to your supplemental new drug application (S-003), dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplemental new drug application proposes revisions to the package insert under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility.**

We also refer to your submission dated July 31, 2002, which constituted a complete response to our February 14, 2002 approvable letter for supplements 058 and 003. This submission includes information regarding our request, in a February 12, 2002 telephone conversation between you and Ms. Maria Walsh of this Division, for historical control incidence of astrocytoma observed in the strain of rat that developed brain astrocytomas in a 52-week chronic toxicity study

in support of your proposal to delete the following

**PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the package insert as recommended in the February 14, 2002 approvable letter:

Our review of the preclinical section of your submission is complete. The information from the Japanese published report of a chronic toxicity study in rats is not from the same testing laboratory as the 52-week chronic toxicity study of omeprazole. In addition, the period of the published study (June 1988 to March 1990) does not correspond to the time of the chronic toxicity study of omeprazole (September 1986 to July 1988). Therefore, this published study does not meet the criteria for historical control incidence data. Also, the background information from the two-year carcinogenicity studies during the period of 1996 to 1999 is not relevant to the findings in the 52-week chronic toxicity study of omepraozle.

We recommend that the information about the finding of brain astrocytomas in the 52-week chronic toxicity study in rats be [redacted] under the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the package insert as recommended in the February 14, 2002 approvable letter.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

Joyce Korvick, M.D.
Deputy Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/
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Joyce Korvick
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DEC 13 2002

NDA 19-810/S-058
NDA 19-810/S-003

**DISCIPLINE REVIEW LETTER**

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs
725 Chesterbrook Blvd.
Mailcode E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your October 7, 1998 supplemental new drug application (S-058) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplemental new drug application proposes revisions to the package insert under PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy,* and *Nursing Mothers*.

We also refer to your supplemental new drug application (S-003) dated November 6, 1989, received November 7, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplemental new drug application proposes revisions to the PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility.*

We also refer to your submission dated July 31, 2002, which constituted a complete response to our February 14, 2002 approvable letter for supplements 058 and 003 and to your August 16, 2002 submission, which included revised draft labeling.

Our review of the clinical section of your submissions is complete. We recommend the following labeling revisions:

**Pregnancy**
**Omeprazole**
*Pregnancy Category C*

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[1]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[2] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number

[1] Friedman JM and Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 200 516.

[2] Kallen BAJ. Use of omeprazole during pregnancy – no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;96(1):63-8.

of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[1] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2-2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[2]
The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study had 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in pregnant rabbits at doses up to 69.1 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

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[1] Ruidómez A, Rodriguez LUG, Cattaruzzi C, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150:476-81.

[2] Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol* 1998;179:727-30.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D.
Deputy Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

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Joyce Korvick
12/13/02 04:43:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-810/S-003 and S-058

AUGAUG 15 2002

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs
725 Chesterbrook Blvd., Mailstop E3-C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

We acknowledge receipt on August 1, 2002 of your July 31, 2002 resubmissions to your supplemental new drug applications for Prilosec® (omeprazole) Delayed-Release Capsules.

These resubmissions contain additional information regarding historical control incidence of astrocytoma observed in the strain of rat that developed astrocytomas in your 52-week toxicity study. This information is submitted in response to the February 12, 2002 telephone conversation between you and Ms. Maria Walsh of this division and to our February 14, 2002 action letter.

With these amendments, we have received complete responses to our February 14, 2002 action letter.

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

Sincerely,

*{See appended electronic signature page}*

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

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

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/s/

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Maria Walsh

8/15/02 10:40:50 AM

Walsh

NDA 19-810/S-058

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mail Code: E-3C
Wayne. PA 19087-5677

AUG 14 2000

Dear Dr. Horowitz:

We acknowledge receipt on August 7, 2000 of your August 4, 2000 resubmission to your supplemental new drug application for Prilosec (omeprazole) Delayed-Release Capsules.

This resubmission contains additional patient information from the Swedish epidemiology study and a re-analysis of the post-marketing spontaneous reports of fetal abnormalities submitted in response to our October 7, 1999 action letter.

With this amendment, we have received a complete response to our October 7, 1999 action letter.

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

Sincerely,

Maria R. Walsh 8/14/00

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

cc:
Archival NDA 19-180/S-058
HFD-180/Div. Files
HFD-180/PM/Walsh

final: M.Walsh 8/10/00
filename: 19810.S058.August-2000.ACKresubmission.doc

RESUBMISSION ACKNOWLEDGEMENT (AC)

WAIL

NDA 19-810/S-058

OCT 21 1999

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your October 7, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplement provides for revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility: Pregnancy;* and *Nursing Mothers*. including a change in the *Pregnancy Category* from *C* to *B*.

We also refer to the not approvable letter dated October 7, 1999 informing you that the epidemiological data submitted in the supplement do not provide adequate information to evaluate the fetal risk from omeprazole exposure during pregnancy.

We further refer to the October 12, 1999 telephone conversation between you and Ms. Maria R. Walsh of this Division in which you requested more detailed information regarding the deficiencies. You stated this information will be helpful to you in preparation for the meeting on November 1, 1999 between representatives of your firm and the FDA to discuss the not approvable action. The deficiencies are listed as follows:

The epidemiologic studies provide little or no information about dose and/or duration of omeprazole therapy, compliance, and concomitant medications and therefore, are inadequate to evaluate the effect of administration of therapeutic courses of omeprazole during pregnancy. While in most instances, mothers gave birth to apparently normal infants. the studies are not designed to allow reliable assessment of the relationship between omeprazole administration and pregnancy outcome.

Although the epidemiologic studies and the spontaneous report data and literature search do not point to any clear association of omeprazole with fetal malformations or spontaneous abortions, the information provided does not constitute an adequate basis for evaluating fetal risk from omeprazole exposure during pregnancy.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

LT 10-21-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 19-810/S-058
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/H.Gallo-Torres
K.Robie-Suh
J.Choudary

Drafted by: M.Walsh 10/18/99
Initialed by: K.Robie-Suh 10/18/99
H.Gallo-Torres 10/20/99
S.Aurecchia 10/20/99
L.Talarico 10/20/99
final: M.Walsh 10/21/99
filename: 19810S58910.ad.doc

ADVICE

WALSH

NDA 19-810/S-058

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

AUG 18 1999

Dear Dr. Horowitz:

Please refer to your pending October 7, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec (omeprazole) Delayed-Release Capsules.

This supplement provides for revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility; Pregnancy;* and *Nursing Mothers*. These revisions include a change in the *Pregnancy Category* from *C* to *B*.

We have completed our review of the Pharmacology section of your submission and have the following comments and information requests:

1. Please clarify whether the reproductive studies conducted [redacted] of Japan were performed in compliance with the U.S. FDA Good Laboratory Practices (GLP) Guidelines. If different regulatory guidelines were used, please specify the deviations from the U.S. FDA GLP Guidelines.

2. Please account for the pregnancy status of all $F_0$ dams (i.e. pregnant, not pregnant, infertile) in Report No. R-120 (Segment II Teratology Study in Rats Using Oral Administration).

3. For the following reports, in which all dams were allowed to deliver their offspring based upon the numbers of implantations, live born fetuses, and stillborn fetuses, there appears to be missing fetuses:

   Report No. R-120 (Segment II Teratology Study in Rats Using Oral Administration).

   Report No. R-249 (Segment II Teratology Study in Rats Using Intravenous Administration).

   Report No. R-361 (Segment III Perinatal and Postnatal Development Study in Rats Using Intravenous Administration).

   Report No. R-143 (Segment III Perinatal and Postnatal Development Study in Rats Using Oral Administration).

Please account for all missing fetuses in these reports.

4. Please provide the line listings for individual dams for the following reports:

   Report No. 241 (Segment I Fertility and Reproductive Performance Study in Rats Using I.V. Administration).

   Report No. 142 (Segment I Fertility and Reproductive Performance Study in Rats Using Oral Administration).

   Report No. 120 (Segment II Teratology Study in Rats Using Oral Administration).

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

KJ 8/18/99

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 19-810/S-058
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/J.Choudary
DISTRICT OFFICE

Drafted by: M.Walsh 8/16/99
Initialed by: J.Choudary 8/17/99
K.Johnson 8/17/99
final: M.Walsh 8/18/99
filename: 19810S58.IR.doc

INFORMATION REQUEST (IR)

NDA 19-810/S-058

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

Dear Dr. Horowitz:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

NDA Number: 19-810

Supplement Number: S-058

Therapeutic Classification: Standard (S)

Date of Supplement: October 7, 1998

Date of Receipt: October 7, 1998

This supplement proposes the following change(s): Revisions to the package insert under PRECAUTIONS, *Carcinogenicity, Mutagenicity, Impairment of Fertility; Pregnancy;* and *Nursing Mothers*. These revisions include a change in the *Pregnancy Category* from *C* to *B*.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 6, 1998 in accordance with 21 CFR 314.101(a). The primary user fee goal date is August 6, 1999. The secondary user fee goal date is October 7, 1999.

All communications concerning this supplemental application should be addressed as follows:

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

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

Sincerely,

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

cc:
Archival NDA 19-810/S-058
HFD-180/Div. Files
HFD-180/PM/M.Walsh
DISTRICT OFFICE

final: M.Walsh 10/19/98
filename: 19810S58810.ack.doc

SUPPLEMENT ACKNOWLEDGEMENT (AC)

25 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-* 19-810
5038 5058

## ITEM 18

## USER FEE COVER SHEET

In accordance with the Prescription Drug User Fee Act of 1997, the attached User Fee Cover Sheet was submitted to the Food and Drug Administration on September 22, 1998, accompanied by a check in the amount of $128,423.00.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Expiration Date: 04-30-01

# USER FEE COVER SHEET

*See Instructions on Reverse Side Before Completing This Form*

1. APPLICANT'S NAME AND ADDRESS

Astra Pharmaceuticals, L.P.
725 Chesterbrook Boulevard
Wayne, PA 19087-5677

2. TELEPHONE NUMBER *(Include Area Code)*

(610 ) 695-1925

3. PRODUCT NAME

PRILOSEC® (omeprazole) Delayed-Release Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

/ /

6. LICENSE NUMBER / NDA NUMBER

19-810

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

***A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.***

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| Marjorie Christie<br>Marjorie Christie, Ph.D. | Director,<br>Regulatory Opertions | Sept. 22, 1998 |

FORM FDA 3397 (5/98)

Created by Business Document Services/CDER/HFD-310