CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-056

OTHER REVIEW(S)

MEMORANDUM

To: **Brian Strongin, RPh, MBA**
Division of Gastroenterology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **October 12, 2007**

Re: **Comments on draft labeling for Prilosec (omeprazole)**
NDA 22-056

We have reviewed the proposed label for Prilosec (FDA version dated 10/3/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- We recommend moving much of the data on use of Prilosec in pediatric patients from its current placement in the label. Because Prilosec is approved for pediatric use in certain conditions, the discussion of the pediatric data should appear in the same places throughout the label as is done for the adult data (e.g., pediatric clinical studies should appear in Clinical Studies, pediatric safety data should be in Adverse Reactions, pediatric pharmacokinetic data should be in Pharmacokinetics). The section "8.4 Pediatric Use" should summarize the available pediatric data upon which the approval was based, and cross-reference to the detailed discussions elsewhere in the label. This section should also summarize any important differences noted between pediatric and adult patients that are relevant for the clinician. Although these recommendations do not stem from any new regulation from the Physician Labeling Rule, they reflect an approach to incorporating pediatric information in labeling agreed upon by OND's SEALD Team and Pediatric and Maternal Health Staff.

- Additionally, we recommend that the Indications and Usage section (in both Highlights and the Full Prescribing Information) explicitly state which indications are approved in children and adults and which ones are approved only in adults.

- We recommend rearranging some of the information about use of clarithromycin and amoxicillin in the label. Specifically, the contraindications about these two drugs should not be included in the Prilosec label's contraindications section, and the warnings/precautions discussions should be modified. There should be a warning/precaution about combination

use with clarithromycin, including all the relevant information, and another one for combination use with amoxicillin. There would also be the warnings/precautions that are specific to omeprazole (i.e., those currently under section 5.3). The topics in this section should be presented in decreasing order of importance, with the most important coming first. Once the ordering of this section has been determined, then a decision must be made regarding how many of them warrant inclusion in Highlights. All may be included, or just the most important ones.

- The section "Recent Major Changes" in Highlights should reflect changes to the Indications and Usage section (the new approved patient population of children ~~2~~) and Dosage and Administration (dosing recommendations in this same population). The text in the FPI that corresponds to these changes must have a vertical line inserted in the left margin next to the new information. b(4)

- We were informed that the labeling change from April 2007 provided for the addition of a new drug interaction. Because this change was not to one of the five sections covered under "Recent Major Changes" (Boxed Warning, Contraindications, Warnings and Precautions, Indications and Usage, and Dosage and Administration), it should not be included under "Recent Major Changes" in Highlights.

- In Contents and in the Full Prescribing Information (FPI), the section and subsection numbers should not have periods after them. Please delete throughout the label.

- Please revise all cross-references in the Full Prescribing Information (FPI) to the preferred formatting for PLR labels, e.g., "*[see Clinical Pharmacology (12.3)]*" and not "*[see Pharmacokinetics (12.3].*" Note that the cross-reference should name the main section heading, but use the appropriate subsection number in parentheses.

- All tables in the label should be titled and consecutively numbered.

HIGHLIGHTS

- This entire section of the label should be in 8 point font (instead of the current 12 point font). This is the minimum allowable font size that will allow Highlights to get as close as possible to the ½ page requirement.

- If, after editing, the Highlights section remains longer than ½ page, the granting of the waiver to this requirement should be included in the approval letter.

- Once the font size is changed to 8 point, the section headers (with the dashes before and after the section names) should be lengthened so the dashes run all the way across the columns with the section title centered within.

- *"HIGHLIGHTS OF PRESCRIBING INFORMATION"*

  This line should appear flush left instead of centered within the left column.

- *"These highlights do not include all the information needed to use PRILOSEC safely and effectively. See full prescribing information for PRILOSEC."*

This sentence should not be italicized. In addition, please insert a hard return after the sentence.

- *"PRILOSEC (omeprazole) DELAYED-RELEASE CAPSULES*
  PRILOSEC (omeprazole magnesium) FOR DELAYED-RELEASE ORAL SUSPENSION"

  We note that these lines are in a different font from the rest of the label. Please correct the font for consistency within the label.

Indications and Usage

- As noted in the general comments above, we recommend that each indication state "in adults" or "in adults and pediatric patients" as appropriate.
- Each line in this section must have a cross-reference in parentheses to the corresponding section of the FPI.
- We recommend that only the first word in each line begin with a capital letter, rather than each word.

Dosage and Administration

- This section must include cross-references to the appropriate section of the FPI. We suggest putting the section number (in parentheses) at the end of each indicated condition.
- In the *H. pylori* section, we recommend indenting the drug names under the two headings, "Triple Therapy" and "Dual Therapy" for ease of reading.
- Under "Frequency" for the *H. pylori* section, we suggest changing "Twice daily for 10 days" to "Each drug twice daily for 10 days" for clarity.
- The acronym "GERD" does not need to be spelled out here because it is defined in the Indications and Usage section.
- *"60 mg (varies with individual patient)"*

  The spacing is odd in this section under "Pathological Hypersecretory Conditions." Please correct.

- *"Pediatric Use*
  to 16 year of age"

  b(4)

  We suggest that this heading be moved all on one line for ease of reading. In addition, please change "year" to "years." We suggest:

  Pediatric Use -16 years of age)

- To be consistent within the section, the two subheadings under "Pediatric Use" should be italicized as is done under the *H. pylori* section instead of bolded.

- As above, the acronym "GERD" can be used here without being spelled out.

- In the pediatric section, we recommend underlining the two column titles ("Weight" and "Dose") for ease of reading.

- Please correct the spacing in the "Weight" and "Dose" rows under Pediatric Use. These table entries would be easier to read if they were spaced better. For example, [redacted] is so tightly spaced that it looks like ' [redacted] Please insert spaces (e.g., [redacted] for ease of reading and to avoid misinterpretation. b(4)

Dosage Forms and Strengths

- This section in Highlights should not include descriptions of the capsule and suspension appearances. Instead, it can read simply:

  PRILOSEC Delayed-Release Capsules: 10 mg, 20 mg, and 40 mg (3)
  PRILOSEC For Delayed-Release Oral Suspension: 2.5 mg and 10 mg (3)

  Note that we have inserted the cross-references to section 3 at the end of each line.

Warnings and Precautions

- As noted above, please revise this section to reflect changes made in the FPI.

- The preferred presentation in this section is to state the risk followed by a colon, and then any further information and clinical recommendations, as appropriate. Please revise accordingly.

Adverse Reactions

- *"Most common adverse reactions (incidence > 1%):"*

  We recommend revising this to read "Most common adverse reactions in adults (incidence >X%): headache, diarrhea..." instead of using a bullet.

- This list is longer than is usually seen in Highlights. Please consider using a higher cut-off rate to reduce the list to the 4-6 most common adverse reactions.

- *"Pediatric use [redacted] to 16 years of age):*
  Adverse event profile resembles adults; however, in pediatric studies, respiratory system events [redacted] were the most frequently reported (8.4)" b(4)

  Do we believe that these high rates of respiratory system reactions [redacted] are truly related to Prilosec use, or are they typical background frequencies in this patient population? Are they worth mentioning in Highlights, or should we say only that the safety profile in pediatric patients was similar to that seen adults?

- *"To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch reactions."* b(4)

  Please delete " from this sentence to comply with the required language in the regulations.

  Please insert a hard return before this sentence to improve readability.

  This sentence should be flush left within the column, not indented.

Drug Interactions

- As with Warnings and Precautions, this section should be reformatted to listing the drug name (or drug class) followed by a colon, and then a description of the interaction or recommended clinical intervention. The current presentation is too wordy and the critical information is not easily accessible. We suggest:

b(4)

Use in Specific Populations

- We suggest deleting the entire bullet about pediatric use because the information will be incorporated into the Indication and Usage section.

- *"Pregnancy: Pregnancy Category C (8.1)"*

  Use of the pregnancy category in Highlights is not recommended because it does not provide adequate information when used alone. Instead, we recommend wording from the labeling regulations such as, "Pregnancy: Use during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus (8.1)" or something similar.

- *"Hepatic Insufficiency:*

b(4)

  For clarity, we suggest revising this bullet to,

Hepatic Impairment: Consider dose reduction, particularly for maintenance of healing of erosive esophagitis (8.X, 12.3)

- The same recommendation applies to the statement on Asian patients.

Patient Counseling Statement

- *"SEE 17 FOR PATIENT COUNSELING INFORMATION"*

  This sentence should not have the dashes surrounding it and should be flush left within the column.

  Please change "SEE" and "FOR" to mixed case lettering to distinguish them from the section title.

Revision Date

- Please ensure that the month/year at the end of Highlights is filled in upon approval of this label (presumable 10/2007)

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.
- A horizontal line should be inserted at the end of Contents, separating it from the FPI.
- If Highlights and Contents cannot fit on one page, then we prefer that Contents appear in its entirety on page 2, instead of splitting it between two pages. As with Highlights, the font size of this section can be smaller to enable it to fit on one page.
- *"Full Prescribing Information: Contents"*

  This line at the beginning of Contents should be bolded and in all upper case letters.

FULL PRESCRIBING INFORMATION

- *"FULL PRESCRIBING INFORMATION"*

  Please make this first line flush left instead of centered on the page.

1 Indications and Usage

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Other Reviews #1

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/s/

Iris Masucci
10/16/2007 09:10:10 AM
DDMAC REVIEWER

Laurie Burke
10/17/2007 05:53:57 PM
INTERDISCIPLINARY

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 22-056

Name of Drug: Prilosec® (omeprazole magnesium) for Delayed-Release Oral Suspension

Applicant: AstraZeneca LP

Material Reviewed:

Submission Date: December 20, 2006

Receipt Date: December 20, 2006

Submission Date of Structure Product Labeling (SPL): December 20, 2006

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

I. Highlights

A. General Comments

1. The sponsor has proposed a Highlights section nearly a full page in length. They have requested a waiver of the ½ page requirement for this section.

The waiver request will be discussed by the review team and a decision to grant or deny it will be made.

2. A blank space has been included below the statement, "HIGHLIGHTS OF PRESCRIBING INFORMATION.

This blank space should be deleted.

3. Blank spaces have been included below all section headings.

These blank spaces should be deleted.

B. The proprietary name, nonproprietary name, and dosage form for Prilosec Delayed-Release Oral Suspension is not listed above the INDICATIONS AND USE section with the listing for Prilosec Capsules.

The proprietary name, nonproprietary name, and dosage form for Prilosec Delayed-Release Oral Suspension should be added following this information for Prilosec capsules.

C. A section for "Recent Major Changes" was not included.

A "Recent Major Changes" section should be added. The full prescribing information (FPI) section title and section number where the changes provided for in NDA 19-810/S-085 (approved April 2007) were added should be listed and the date, "4/07" should be added.

D. The statement, "Revised 11/2006" at the end of the Highlights section should be changed to the month/year the NDA is approved.

Change the statement "Revised 11/2006" at the end of the Highlights section to "Revised 10/2007".

II. Full Prescribing Information: Contents

The sponsor has included periods after all section and subsection numbers.

Periods after section and subsection numbers should be deleted.

III. Full Prescribing Information

A. General Comments

1. References are not listed correctly.

The preferred presentation of cross-references in the FPI is the section (not

subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.

2. Periods are included after section and subsection numbers

   Periods after section and subsection numbers should be deleted.

3. Numbers to one decimal place have been included throughout the label.

   Numbers should be rounded to one digit unless they are meaningful at one decimal place.

B. Drug Interaction section

The language provided for in the April 27, 2007 approval letter for NDA 19-810/S-085 was not included in this section.

The sponsor should add the language provided in the April 27, 2007 approval letter for NDA 19-810/S-085.

C. How Supplied/Storage and Handling

The manufacturer information, "Manufactured for: AstraZeneca LP, Wilmington, DE 19850" located at the end of this section should be placed after the Patient Counseling Information section.

The sponsor should move the statement, "Manufactured for: AstraZeneca LP, Wilmington, DE 19850", to the end of the package insert, after the Patient Counseling Information section.

Recommendations

Please address the identified deficiencies/issues listed above in bold and re-submit labeling as soon as possible. This updated version of labeling will be used for further labeling discussions.

Supervisory Comment/Concurrence:

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

Drafted: BKS/September 28, 2007
Finalized: BKS/October 1, 2007
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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

/s/

Brian Strongin
10/1/2007 09:47:49 AM
CSO

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-171

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

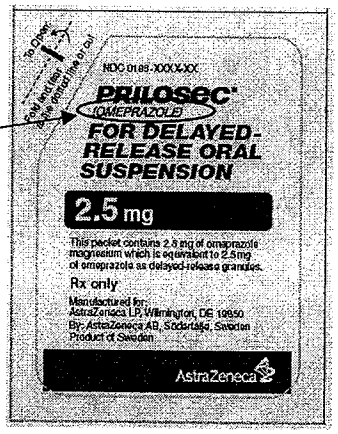
Date: April 17, 2007

OSE Review # 2007-423, Prilosec (Omeprazole for Delayed-release Oral Suspension), 2.5 mg and 10 mg
NDA 22-056

This memorandum is in response to a February 20, 2007 request from your Division for a review of the container labels, carton and package insert labeling for Prilosec delayed released oral suspension.

the review of container labels of Prilosec, DMETS has focused on safety issues relating to medication errors. The only comment DMETS has is that the active ingredient omeprazole is small and not noticeable on the label. Please increase the prominence of the established name so that it commensurate with the prominence of the proprietary name and the dosage form. Additionally, ensure that the prominence of the established name is at least ½ the size of the proprietary name per CFR 21 201.10(g)(2).

Increase in prominence and ensure that the established name is ½ the size of proprietary name.



Prilosec for Delayed-release Oral Suspension 2.5 mg Packet Label

In summary, DMETS recommends the above labeling change. DMETS recommends submission of the revised tainer label and carton labeling when they are available for review and comment. If you have further questions or ced clarification, please contact Nancy Clark at 301-796-1187.

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/s/

Linda Kim-Jung
5/4/2007 09:32:40 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Kristina Arnwine 5/4/07.

Denise Toyer
5/4/2007 01:03:45 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/4/2007 02:11:15 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: July 19, 2007

FROM: C.T. Viswanathan, Ph.D. CTV 7/20/07
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-056, Prilosec (Omeprazole magnesium) Delayed-Release for Oral Suspension, 2.5mg and 10mg, Sponsored by AstraZeneca LP

TO: Brian Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products (DGP)

At the request of DGP, the Division of Scientific Investigations (DSI) conducted audits of the clinical and analytical portions of the following bioequivalence study:

Study D9586C00002: A Phase I, Open, Randomized, Three-Way Crossover, Single-Center Bioavailability Study Comparing Three Different Formulations of Omeprazole, 20 mg Following Single and 5 Days Repeated Once Daily Oral Administration in Healthy Male and Female Subjects.

The clinical portion of the study was conducted at AstraZeneca Clinical Pharmacology Unit, Sahlgrenska University Hospital, Gothenburg, Sweden, and the analytical portion was conducted at ——— b(4)

Following the inspections at AstraZeneca Clinical Pharmacology Unit (5/28-30/07) and ——— (6/4-5/07), Form 483s were issued. DSI's evaluation of the significant items and the firm's response (Attachment 1) follows:

Clinical Site: AstraZeneca Clinical Pharmacology Unit, Sahlgrenska University Hospital, Gothenburg, Sweden

a. Following discrepancies were noted with the electronic database (AMOS)*.

i. For some records, the source documents are also eCRF and verification of such records were not possible.

AMOS constitutes both as source document and eCRF for concomitant medication. The inspection revealed discrepancies between concomitant medications reported in AMOS and the data listings in the clinical report. For example, data listing indicates that Panodil® was administered to Subjects 2 and 22 on March 2 and April 24 of 2006, respectively. However, Panodil® was not listed in AMOS for the above subjects.

ii. Failure to demonstrate that audit trail records exist in AMOS System at this site.

There was no evidence of an audit trail for changes made to data in AMOS. The site stated that they do not have permission to access AMOS. The sponsor restricted access of the audit trail records to principal investigator.

Analytical Site: _____ b(4)

b. Failure to document that the light sensitive reference standard was processed in a protected environment. (Item 5, Form 483)

There were no written procedures or other documentation during the study to assure that the light sensitive omeprazole reference standard was handled in a light protected environment. _____ concurred with the finding but maintained that that the reference standards were handled in a protected environment. b(4)

c. Failure to use a proper QC range to support the study subject sample drug concentrations. (Item 1, Form 483)

The QC concentrations at 50, 500 and 6000 nmol/L were used for the study. As the majority of the subject plasma

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*AstraZeneca used an electronic database (AMOS), which serves as electronic CRF data (eCRF) and, in some cases, also as source data. AMOS serves as eCRF for dosing, blood sampling, ECG and laboratory reports as these data were first captured elsewhere. In contrast, AMOS also serves as source documents for medical history, physical exams and concomitant medication as these data were captured directly into AMOS. Data was first captured using an electronic data capture system (EDCS) for 9 subjects and on paper for remaining 15 subjects

concentrations was less than 2000 nmol/L, the high QC concentration was not representative of the subject plasma concentrations. Less than 0.5% (5 of 2116) of subject plasma samples had omeprazole concentrations >4000 nmol/L.

d. **Selective changes were made in several chromatograms without establishing SOPs.** (Item 2, Form 483)
Injection volumes were changed, chromatographic peaks were deleted, and integration time windows were changed for several subject samples without established criteria. In their response, ——— maintained that same injection volume was used in all runs. Also, ——— stated that only peaks outside the retention time windows were deleted to avoid detecting the wrong peaks, and integration time windows were changed when a new mobile phase was used to ensure that the correct retention times were used. However, ——— response could not be confirmed during the inspection and there were no established procedures for making such changes. b(4)

e. **Selective manual integrations on several runs. Failure to maintain SOP.** (Item 3, Form 483)
The inspection revealed that manual re-integrations were performed in several runs without established criteria. ——— responded that manual re-integrations were performed to obtain correct baseline. However, this could not be confirmed during the inspection as several chromatograms were manually re-integrated. b(4)

f. **Failure to include the raw data for stability in the final report.** (Item 6, Form 483)
——— validation report did not include the freeze-thaw (F-T), bench-top (B-T) and long-term (L-T) stability results Summary of the stability results was provided during the inspection. However, ——— did not have the raw data to support the stability results. ——— stated that the relevant stability data was collected by the sponsor. Therefore, analyte stability could not be confirmed during the inspection. b(4)

g. **Failure to scan the study subject plasma samples shipped from the sponsor and confirm the ID.** (Item 4, Form 483)
In their response, ——— stated that they did not scan or use the barcodes on the subject plasma sample tubes, as the barcodes were for the sponsor's internal use. ——— maintained that they confirmed the subject ID information against the submission sample list upon receipt and during the time of analysis. However, the inspection found no b(4)

documentation that subject sample IDs were verified upon receipt.

h. **Failure to maintain documentation as to when samples were removed from the freezer and returned and by whom.** (Item 7, Form 483)
There was no documentation of the time and the individuals removing and returning subject samples from the freezer. ——— acknowledged that sample removal and return times were not recorded, only the dates were recorded. b(4)

i. **Failure to maintain documents sequentially with regard to date.** (Item 8, Form 483)
Data entries in the laboratory notebook were not in sequential order with regard to date.

——— in their response stated that they have revised existing procedures and instituted new procedures to correct the objectionable findings (i.e. b to i) for future studies. b(4)

Conclusions:

The accuracy of omeprazole concentrations in subject samples in Study D9586C00002 cannot be assured due to the widespread deficiencies in analytical conduct (findings b. to i.).

After you have reviewed this memo, please append it to the original NDA submission.

Final Classifications:
VAI: AstraZeneca Clinical Pharmacology Unit,
Sahlgrenska University Hospital, Gothenburg, Sweden
VAI: ——— b(4)

cc:
HFD-45/RF
HFD-48/Himaya/Subramaniam(2)/CF
OND/ODEIII/DGP/Barraco/NDA 22-056
HFD-880/Bashaw
HFR-CE650/Sadiku
Draft: SS 7/10/07
Edit: CTV b(4)
DSI: ——— .\BE\eircover\22056ast.ome doc
FACTS ID ———

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other- 2

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/s/

Sriram Subramaniam
7/20/2007 05:15:50 PM
PHARMACOLOGIST
Sent on behalf of Dr. Viswanathan

Barr ACO

MEMORANDUM

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

DATE: March 13, 2007

TO: Associate Director
International Operations Drug Group
Division of Field Investigations (HFC-130)

FROM: C.T. Viswanathan, Ph.D. CTV 3/16/07
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

THROUGH: Gary Della'Zanna, D.O. M.Sc.
Director
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2007, **High Priority CDER PDUFA NDA, Pre-Approval Data Validation**, Bioresearch monitoring, Human Drugs, CP 7348.001

RE: NDA 22-056
DRUG: Prilosec (Omeprazole magnesium) Delayed-Release for Oral Suspension, 2.5mg and 10mg
SPONSOR: AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355
Sponsor's Contact: George A. Kummeth
Global Director, Regulatory Affairs
Tel: (302) 885-8415

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **Due to the user fee deadline, the inspections should be completed by June 20, 2007.**

Study D9586C00002: "A Phase I, Open, Randomized, Three-Way Crossover, Single-Center Bioavailability Study Comparing Three Different Formulations of Omeprazole, 20mg Following Single and 5 Days Repeated Once Daily Oral Administration in Healthy Male and Female Subjects".

Clinical Site: AstraZeneca Clinical Pharmacology Unit
Sahlgrenska University Hospital
S-413 45 Gothenburg, Sweden
TEL: 031-706 51 55
Mobile: 0707-88 11 83

Clinical Investigator: Jacob Odenstedt, M.D.

The study was conducted to evaluate the bioavailability of a new omeprazole sachet formulation [Prilosec (omeprazole magnesium) for Delayed-Release Oral Suspension] in relation to the marketed Prilosec capsules and the omeprazole suspension used in pediatric studies. In the study, 24 subjects received 5 days repeated doses of omeprazole 20 mg, either as a sachet formulation, suspension or commercial Prilosec capsule under fasting conditions.

Please have the records of all study subjects audited. **Please note that the study data was primarily captured at the site by immediate data entry onto the database. In cases where immediate data entry into the database was not possible, data were first recorded on a paper CRF page, and thereafter entered into the database. Please verify the accuracy of the transcribed data.**

The subject records in the FDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. **Dosing logs must be checked to confirm that correct drug products were administered to the subjects.** Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Please check the batch numbers of both the test and the reference drug formulations used in the studies with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Analytical Site:

b(4)

b(4)

Contact Person:

Instrumentation: LC/UV

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The actual assay of the subject plasma samples, as well as the variability between and within runs, QC, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background material will be forwarded directly. **A scientist from the GLP and Bioequivalence Investigations Branch Team in DSI with specialized knowledge will participate in the inspection.**

Headquarters Contact Person: Nilufer M. Tampal, Ph.D.
(301) 594-2457

cc:
HFD-45/RF
HFD-48/Tampal/Himaya/CF
HFD-180/Barraco (NDA 22-056)
HFR-134/Kadar (please fax a copy 301-443-6919)
Draft: NMT 03/09/07
Edit: MKY MKY 3/13/07
DSI — O:\BE\assigns\bio22056.doc b(4)
FACTS —