

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022283Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-283

NAME OF APPLICANT / NDA HOLDER

Schering-Plough HealthCare Products, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Zegerid® OTC Powder for Oral Suspension

ACTIVE INGREDIENT(S)

STRENGTH(S)

Omeprazole
Sodium Bicarbonate

Omeprazole 20 mg
Sodium Bicarbonate 1680 mg

DOSAGE FORM

Powder for Oral Suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,489,346 B1

b. Issue Date of Patent

December 3, 2002

c. Expiration Date of Patent

July 15, 2016

d. Name of Patent Owner

The Curators of the University of Missouri

Address (of Patent Owner)

615 Locust Street, Building 304F

City/State

Columbia, MO

ZIP Code

65211

FAX Number (if available)

(573) 882-1130

Telephone Number

(573) 882-2821

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States 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 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Schering-Plough HealthCare Products, Inc., the applicant has a place of business in the U.S.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

3. Drug Substance (Active Ingredient)

3.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

3.3 If the answer to question 3.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

3.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 3.3.

3.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

3.6 Does the patent claim only an intermediate? Yes No

3.7 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Drug Product (Composition/Formulation)

4.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

4.2 Does the patent claim only an intermediate? Yes No

4.3 If the patent referenced in 4.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 24, 26, 31 - 35, 37, 49-53, 55, 56, and 91 - 94 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
See Attachment 1.

No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

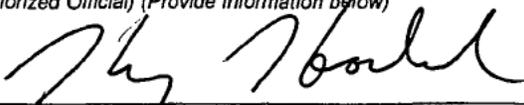
6. Declaration Certification

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Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



3/3/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Henry Hadad

Address

SCHERING CORPORATION, Patent Dept., K-6-1-1990
2000 Galloping Hill Road

City/State

Kenilworth, New Jersey

ZIP Code

07033-0530

Telephone Number

(908) 298-2906

FAX Number (if available)

(908) 298-5388

E-Mail Address (if available)

henry.hadad@spcorp.com

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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Zegerid® OTC Powder for Oral Suspension

ACTIVE INGREDIENT(S)

STRENGTH(S)

Omeprazole
Sodium Bicarbonate

Omeprazole 20 mg
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DOSAGE FORM

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1. GENERAL

a. United States Patent Number 6,699,885 B2	b. Issue Date of Patent March 2, 2004	c. Expiration Date of Patent July 15, 2016
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d. Name of Patent Owner The Curators of the University of Missouri	Address (of Patent Owner) 615 Locust Street, Building 304F	
	City/State Columbia, MO	
	ZIP Code 65211	FAX Number (if available) (573) 882-1130
	Telephone Number (573) 882-2821	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States 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 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) <input checked="" type="checkbox"/> Schering-Plough HealthCare Products, Inc., the applicant has a place of business in the U.S.	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

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3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 1-11, 13-18, 23 - 25 and 26 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
See Attachment 1.

No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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Date Signed



3/3/08

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Henry Hadad

Address

SCHERING CORPORATION, Patent Dept., K-6-1-1990
2000 Galloping Hill Road

City/State

Kenilworth, New Jersey

ZIP Code

07033-0530

Telephone Number

(908) 298-2906

FAX Number (if available)

(908) 298-5388

E-Mail Address (if available)

henry.hadad@spcorp.com

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Zegerid® OTC Powder for Oral Suspension

ACTIVE INGREDIENT(S)

STRENGTH(S)

Omeprazole
Sodium Bicarbonate

Omeprazole 20 mg
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DOSAGE FORM

Powder for Oral Suspension

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1. GENERAL

a. United States Patent Number

6,780,882 B2

b. Issue Date of Patent

August 24, 2004

c. Expiration Date of Patent

July 15, 2016

d. Name of Patent Owner

Address (of Patent Owner)

615 Locust Street, Building 304F

City/State

Columbia, MO

ZIP Code

65211

FAX Number (if available)

(573) 882-1130

Telephone Number

(573) 882-2821

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States 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 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

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E-Mail Address (if available)

Schering-Plough HealthCare Products, Inc., the applicant has a place of business in the U.S.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

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Patent Owner

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Name

Henry Hadad

Address

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2000 Galloping Hill Road

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Kenilworth, New Jersey

ZIP Code

07033-0530

Telephone Number

(908) 298-2906

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(908) 298-5388

E-Mail Address (if available)

henry.hadad@spcorp.com

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1. GENERAL

a. United States Patent Number

6,645,988 B2

b. Issue Date of Patent

November 11, 2003

c. Expiration Date of Patent

July 15, 2016

d. Name of Patent Owner

Address (of Patent Owner)

615 Locust Street, Building 304F

City/State

Columbia, MO

ZIP Code

65211

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Schering-Plough HealthCare Products, Inc., the applicant has a place of business in the U.S.

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

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2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



3/3/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Henry Hadad

Address

SCHERING CORPORATION, Patent Dept., K-6-1-1990
2000 Galloping Hill Road

City/State

Kenilworth, New Jersey

ZIP Code

07033-0530

Telephone Number

(908) 298-2906

FAX Number (if available)

(908) 298-5388

E-Mail Address (if available)

henry.hadad@spcorp.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

Paragraph IV Certification

Pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act and the Food Drug Administration regulations codified in 21 CFR §314.50(i)(1)(i)(A)(4), Schering-Plough HealthCare Products, Inc. hereby certifies with respect to each of United States Patent Numbers 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, 6,428,810 that such patents are invalid or will not be infringed by the manufacture, use or sale of Zegerid OTC™ Omeprazole/Sodium Bicarbonate Powder for Oral Suspension, for which the §505(b)(2) application is being submitted.

Pursuant to 21 CFR §314.50(i)(1)(i)(A)(4), Schering-Plough Healthcare Products, Inc. certifies that the owners of United States Patent Numbers 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, 6,428,810 and the holder of the approved New Drug Application 21-229 will be sent notification of non-infringement and/or invalidity of the above-referenced patents as required by 21 CFR §314.52(a) that contains the information described in 21 §CFR 314.52(c).



Henry Hadad
Vice President, Assoc. General Counsel

March 10, 2008

Date

Schering-Plough HealthCare Products hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



John O'Mullane, Ph.D
Group Vice President, Research and Development
Schering-Plough HealthCare Products, Inc.



Date



SCHERING-PLOUGH

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-283 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DNCE PDUFA Goal Date: 01-20-09 Stamp Date: 03-20-08

Proprietary Name: Zegerid OTC

Established/Generic Name: Omeprazole 20mg and Sodium Bicarbonate 1680 mg

Dosage Form: powder for oral suspension

Applicant/Sponsor: Schering-Plough

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
 - (2) _____
 - (3) _____
 - (4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treats frequent heartburn (occurs 2 or more days per week).

Q1: Is this application in response to a PREA PMC/PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMC/PMR #: _____

Does the division agree that this is a complete response to the PMC/PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification: It is clinically inappropriate for Zegerid to be available OTC for pediatric patients up to 18 years of age. Pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux be examined by physicians for possible complications, and the treatment of frequent heartburn in the pediatric population should be under the direction of a physician. The OTC availability of Zegerid and other proton pump inhibitors (PPI) would be counter to this indication. Omeprazole is the only currently approved PPI for OTC use, and it is not approved for patients 17 years of age and younger.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition **AND** (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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/s/

Mary R Vienna
12/10/2008 09:05:16 AM

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Wednesday, April 03, 2013 7:27 AM
To: 'verna.mecadon@merck.com'
Subject: NDA 22283

Good morning Ms. Mecadon,

We are reviewing your New Drug Application # 22283 that mentions the following sites as the manufacturing, packaging, testing and control operations for Zegerid OTC™ Powder for Oral Suspension.

Please indicate the type of testing that will be performed on the following sites:



Please submit the information requested by email to me (Luz.E.Rivera@fda.hhs.gov) .

Please acknowledge the receipt of this request

Thank you,
Luz E Rivera, Psy.D.
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301) 796-4013

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/s/

LUZ E RIVERA
04/10/2013

Buchanan, Jeffrey A.

From: Buchanan, Jeffrey A.
Sent: Wednesday, January 16, 2013 2:20 PM
To: Mecadon, Verna
Cc: Buchanan, Jeffrey A.
Subject: NDA 022283 Zegerid OTC - SD-43 - Recd 12/17/12 - Information Request

Importance: High

Hello Ms. Mecadon,

Please see the following request for information and respond to the request by January 28, 2013. If you have questions, please contact me. Thank you!

NDA 022283 Zegerid OTC - Information Request regarding Class 2 Resubmission (submitted December 14, 2013)

The content of the annotated draft labeling text (section 1.14.1.2) and the draft labeling text (section 1.14.1.3) do not reflect the content of the labels submitted in section 1.14.2.1. Specifically, the submission contains label language that was omitted or revised in previous review cycles of this application, including:

1. For all labels, the (b) (4) text described in the annotated and draft labeling text was removed in previous reviews and is absent on the submitted labels.
2. For all labels, the purpose statement of Sodium Bicarbonate as an (b) (4) in the principal display panel (PDP) and drug facts label described in the annotated and draft labeling text was amended in previous reviews to "Allows absorption of this omeprazole product" as stated on the submitted labels.
3. The annotated and draft labeling text states there is (b) (4) which is absent on submitted carton labels.
4. The packet net weight is included on the PDP of all submitted labeling, but is not included in the annotated and draft labeling submission.
5. The product described as (b) (4) in the annotated and draft labeling submission appears as Zegerid OTC® on the submitted labels.
6. "How Zegerid OTC Works for Your Frequent Heartburn" content and "Tips for Managing Heartburn" content is on the submitted labels but not included in the annotated and draft labeling text.
7. The annotated and draft labeling text includes the (b) (4) which was removed in previous reviews and replaced with "Tips for Managing Heartburn" on the carton labels. (b) (4)

Under 8. **Directions** in the drug facts label, the annotated and draft labeling text states that the first bullet under **14-Day Course of Treatment** reads as (b) (4) In previous review cycles, this language was revised to "[bullet]

product should be taken at least 1 hour before eating in the morning” as stated on the submitted labels.

9. Under the **Directions** section of the drug facts label, the annotated and draft labeling text states that the last bullet reads as “[bullet] children under 18 years of age: ask a doctor”. In previous review cycles, this language was revised to “[bullet] children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition.” as stated on the submitted labels.
10. Under the **Other Information** section of the drug facts label, references to [REDACTED] (b) (4) are still present on the second and third bullet of the annotated and draft labeling text and are absent in the submitted labels.
11. Under the **Questions or comments?** section of the drug facts label, the dates and times information for calling the toll free number are missing in the annotated and draft labeling submission, but are included in the submitted labeling.
12. For the one-dose immediate container, the annotated and draft labeling submission states that the directions on the back panel state [REDACTED] (b) (4) while the submitted label states “READ OUTER CARTON FOR WARNINGS AND COMPLETE PRODUCT INFORMATION.”
13. For the one-dose immediate container, the directions on the top right corner of the front panel in the annotated and draft labeling submission states [REDACTED] (b) (4) with the illustrations of scissors, while the submitted label states “FOLD AT LINE. TEAR AT ARROW” with no scissors illustration.
14. For the 2-count sample carton PDP, the language, illustrations and directions submitted in the annotated and draft labeling text do not match the PDP of the submitted 2-count carton label.
15. For the 2-count sample carton, the language for the right and left panels described in section 2.1.3 of the annotated and draft labeling text do not match the text of the right and left panels of the submitted 2-count carton label.
16. For the 2-count sample carton, the language for the bottom panel described in section 2.1.4 of the annotated and draft labeling text does not match the text of the bottom panel of the submitted 2-count carton label.

Please submit annotated draft labeling text and draft labeling text that is aligned with the submitted labels by January 28, 2013.

Jeff Buchanan

Consumer Safety Officer/RPM
Division of Nonprescription Clinical Evaluation (DNCE)
FDA/CDER/OND, Office of Drug Evaluation IV
10903 New Hampshire Ave., WO22 Room 5473
Silver Spring, MD 20903
Phone: 301-796-1007 Fax: 301-796-9899
jeffrey.buchanan@fda.hhs.gov

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/s/

JEFFREY A BUCHANAN
01/16/2013

Vienna, Mary R

To: Mecadon, Verna
Subject: Notification of Tracked Safety Issue, proton pump inhibitors

Dear Ms. Mecadon,

FDA staff in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) regularly conduct routine safety monitoring. When a **potential** signal of a serious risk of an FDA-approved drug or biologic product is identified (from various sources, such as our Adverse Event Reporting System (AERS) database, the literature, or regulatory submission), a Tracked Safety Issue is created in CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) to provide a comprehensive regulatory history of the potential safety issue.

We created a new DARRTS Tracked Safety Issue (TSI) on November 23, 2011 for the following products regarding clostridium difficile-associated diarrhea.

NDA 022281, Zegerid OTC® (omeprazole magnesium 20mg & sodium bicarbonate 1100 mg) capsule
NDA 022283, Zegerid OTC® (omeprazole magnesium 20mg & sodium bicarbonate 1680 mg) powder for oral suspension

As you may know, Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355). This section in FDAAA, among other things, directs FDA to "post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by the Adverse Event Reporting System within the last quarter."

Currently, to comply with Section 921 of FDAAA, the Agency reviews all DARRTS TSIs that have been created each quarter, and those TSIs that are based wholly or in part on AERS data are posted in the corresponding quarter on the AERS web site. Therefore, if your safety issue is based wholly or in part on AERS data, it will be included the fourth quarter posting for 2011.

Additional information on Section 921 and the quarterly reports are available at http://www.fda.gov/Cder/aers/potential_signals/default.htm.

If you have any questions, call Sherry Stewart at 301-796-9618.

Sincerely,

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

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/s/

MARY R VIENNA
01/26/2012

From: [Vienna, Mary R](#)
To: ["Midgette, Paulette"](#)
Cc: [Jappar, Dilara](#)
Subject: Information request for NDA 22-283/Zegerid powder
Date: Tuesday, November 22, 2011 10:18:49 AM

Hi Paulette;

This is another information request for the above NDA:

The application states that you have established omeprazole stock solution stability for 121 day at 4°C where omeprazole stock stability evaluation of 97 and 168 days at 4°C were rejected as they were not within acceptance criteria. It is uncertain to us that how the omeprazole stock stability can be established for 121 days while it was not stable for the shorter period of time of 97 days.

Please clarify how long the stock was actually stored before usage. Please also provide stock stability data for 97 and 168 days where the stock stability were not within acceptance criteria, as well as the stock stability data for 36, 50, 111, and 121 days where stock stability were within acceptance criteria according to your bioanalytical validation report.

Please let me know if you have any questions.

Thanks.

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

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/s/

MARY RUSSELL R VIENNA
11/30/2011

From: [Vienna, Mary R](#)
To: ["Midgette, Paulette"](#)
Cc: [Scroggs, Betsy](#)
Subject: NDA 22-283 Zegerid OTC Powder Information Request
Date: Monday, November 21, 2011 12:32:58 PM
Importance: High

Hi Paulette;

For NDA 22-283, Zegerid OTC Powder, please confirm the location of the lot and expiration information on the Packet (1-dose) immediate container labeling.

Thank s so much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

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/s/

MARY RUSSELL R VIENNA
11/30/2011

From: [Vienna, Mary R](#)
To: ["Midgette, Paulette"](#)
Bcc: [Furness, Melissa](#); [Lee, Sue Chih H](#); [Jappan, Dilara](#)
Subject: Information request for NDA 22-283/Zegerid OTC powder for solution
Date: Wednesday, November 16, 2011 3:29:32 PM
Importance: High

Hi Paulette;

Our reviewer is analyzing your September submission, and the data does not include information regarding whether the subjects received Zegerid or Prilosec. It is also unclear as to whether GPI or GPII stands for treatment with Zegerid or Prilosec. In addition, the data also does not contain information on the treatment sequence, which is needed to run the analysis.

As we indicated in our September 16 information request, we need the patient ID number, treatment, treatment sequence, period, dose, demographics, concentration at each time point and PK parameters for each patient in order to reanalyze the data.

We need the missing information immediately, as we have less than two weeks to complete the review.

Thanks very much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
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Mary.Vienna@fda.hhs.gov

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/s/

MARY RUSSELL R VIENNA
11/30/2011

From: [Vienna, Mary R](#)
To: [Midgette, Paulette](#)
Bcc: [Jappar, Dilara](#); [Lee, Sue Chih H](#); [Chang, Christina](#); [Shetty, Daiva](#)
Subject: Information request for NDA 22-283/Zegerid OTC powder for solution
Date: Friday, September 16, 2011 1:55:58 PM
Importance: High

Hi Paulette;

I have the following information request for this NDA:

Submit the PK data set for review. This will include the patient ID number, treatment, treatment sequence, dose, demographics, concentration at each time point, and PK parameters for each patient.

We need this information immediately. Please contact me if you have any questions.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

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/s/

MARY RUSSELL R VIENNA
11/30/2011

From: [Vienna, Mary R](#)
To: ["Midgette, Paulette"](#)
Cc: [Scroggs, Betsy](#)
Subject: NDA 22-283 Zegerid OTC Powder Information Request
Date: Monday, November 21, 2011 12:32:58 PM
Importance: High

Hi Paulette;

For NDA 22-283, Zegerid OTC Powder, please confirm the location of the lot and expiration information on the Packet (1-dose) immediate container labeling.

Thank s so much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
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Mary.Vienna@fda.hhs.gov

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/s/

MARY RUSSELL R VIENNA
11/30/2011



NDA 022281

NDA 022283

(b) (4)

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

MSD Consumer Care, Inc.
Attention: Paulette Midgette, M.S.
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Midgette:

We acknowledge receipt on April 6 and April 12, 2011, of your April 5 and April 12, 2011 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Schering-Plough Healthcare Products, Inc.
556 Morris Avenue
Summit, NJ 07901

to

MSD Consumer Care, Inc.
556 Morris Avenue
Summit, NJ 07901

for the following new drug applications:

NDA 022281 Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1100mg) capsules

NDA 022283 Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1680) powder

(b) (4)

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have Drug Master Files (DMFs) referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their DMF(s).

NDA 022281

NDA 022283

(b) (4)

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Mary R. Vienna
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MARY RUSSELL R VIENNA
10/06/2011



NDA 022283

INFORMATION REQUEST

MSD Consumer Care, Inc.
Attention: Paulette Midgette, M.S.
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Midgette:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1680) powder for oral suspension.

We also refer to your June 29, 2011 submission, containing a complete, class 2 response to our July 12, 2010, action letter.

We are reviewing the clinical pharmacology and labeling sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

CLINICAL PHARMACOLOGY

1. Submit long-term stability data at -20°C as referenced in the bioanalytical study report.
2. Submit report on extract stability of at least 59 hours as referenced in the bioanalytical study report.
3. Provide information on the sample collection date and the sample analysis date.

LABELING

1. Move the "sample not for sale" statement on the 2-count sample carton from the right flap to the Primary Display Panel, to be consistent with other OTC sample cartons.

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MARY RUSSELL R VIENNA
10/04/2011
signed for Melissa Hancock Furness



NDA 022281
NDA 022283

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MSD Consumer Care, Inc.
Attention: Paulette Midgette, M.S.
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Midgette:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 022281 Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1110mg) capsule
NDA 022283 Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1680mg) powder

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability,

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MELISSA H FURNESS

09/15/2011

Signing for Dr. Andrea Leonard-Segal



NDA 022283

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

MSD Consumer Care, Inc.
Attention: Paulette Midgette, M.S.
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Midgette:

We acknowledge receipt on June 30, 2011, of your June 29, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zegerid® OTC (omeprazole 20mg/sodium bicarbonate 1680) powder for oral suspension.

We consider this a complete, class 2 response to our July 12, 2010, action letter. Therefore, the user fee goal date is December 30, 2011.

If you have any questions, call me at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Mary R. Vienna
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MARY RUSSELL R VIENNA
07/21/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022283

MEETING MINUTES

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid[®] OTC (omeprazole 20 mg & sodium bicarbonate 1680 mg) powder for oral suspension.

We also refer to the telecon between representatives of your firm and the FDA on August 24, 2010. The purpose of the meeting was to discuss FDA comments made in the Complete Response letter of July 12, 2010.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mary Vienna, Regulatory Project Manager at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 24, 2010

TIME: 12:30 – 1:30 p.m. EST

LOCATION: Teleconference

APPLICATION: NDA 022283

DRUG NAME: Zegerid® OTC (omeprazole 20mg & sodium bicarbonate 1680 mg) powder for oral suspension

TYPE OF MEETING: Type A

MEETING CHAIR: Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation

MEETING RECORDER: CAPT Mary Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES:

Division of Nonprescription Clinical Evaluation

Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Christina Chang, M.D., M.P.H. Medical Officer
Melissa Hancock Furness, Chief, Project Management Staff
CAPT Mary Vienna, R.N., M.H.A., Regulatory Project Manager
LT CDR Jessica Diaz, R.N., Regulatory Project Manager
LT Phong Do, Pharm D., Regulatory Project Manager

Office of Clinical Pharmacology and Biopharmaceutics

CAPT E. Dennis Bashaw, PharmD., Director, Division of Clinical Pharmacology-3
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Schering Plough Healthcare Products, Inc.

John O'Mullane, Ph.D., Group Vice President, R&D

Stephenie Barba, Vice President, Regulatory Affairs

Paul Starkey, M.D., Senior Director, Medical Affairs

Sharon Olmstead, Vice President, Global Regulatory Affairs, U.S. Policy and Intelligence

Dennis Nelson, Ph.D., Vice President, R&D OTC Medicines

Ajmal Khan, Ph.D., Research Fellow

Bill Cochran, Senior Manager, Regulatory Affairs

1.0 BACKGROUND:

On March 19, 2008, Schering Plough Healthcare Products, Inc. (Schering) submitted a new drug application (NDA 22-283) for Zegerid OTC (omeprazole 20mg and sodium bicarbonate 1680mg) powder for oral suspension. FDA issued Complete Response action letters on January 16, 2009 and July 12, 2010 respectively.

Schering submitted a meeting request to the FDA for a type A meeting on August 5, 2010 to discuss FDA comments made in the July 12, 2010 Complete Response letter.

In the meeting package submitted on August 5, 2010, Schering provided an outline for a proposed two-arm, crossover PK study which directly compares Zegerid OTC (omeprazole 20 mg and sodium bicarbonate 1680 mg) powder to prescription Prilosec (omeprazole) 40 mg capsule for FDA comment.

2.0 MEETING OBJECTIVES:

To obtain FDA feedback and guidance on the data required to address the deficiencies identified in the July 12, 2010 Complete Response letter.

3.0 DISCUSSION:

Preliminary responses to the questions enclosed in the August 5, 2010 meeting package were sent to Schering via e-mail on August 18, 2010. These questions and preliminary FDA responses are listed below in italics. A record of the discussion that occurred during the meeting is presented following the question and response to which the discussion pertained. For all other questions, Schering acknowledged the FDA response and there was no further discussion on that point during the meeting.

3.1 Question 1

In the July 12, 2010 Complete Response letter the Agency stated the following:

Perform a PK study to demonstrate that the C_{max} and AUC of Zegerid OTC Powder for Oral Suspension is less than that of Prilosec 40 mg Capsules. This would involve a 3-arm study comparing Zegerid OTC 20 mg powder, with the Prilosec OTC 20 mg tablet and prescription Prilosec 40 mg capsule under fasted conditions. We recommend that you submit any protocols to us for review and comment before proceeding.

As has been demonstrated by previous PK data, C_{max} and AUC of Zegerid OTC Powder for Oral Suspension will be higher than Prilosec OTC Tablets. Thus SPHCP proposes a 2 arm study comparing Zegerid OTC Powder for Oral Suspension to Prescription Prilosec 40 mg Capsules.

The following is an outline of the proposed study design:

- Standard PK comparative study
- Fasted Conditions
- 24 patients
- 2 Component (Zegerid OTC Powder for Oral Suspension and Prescription Prilosec 40 mg Capsules) cross-over design.
- A successful outcome will show that with respect to both point estimate and upper 90% confidence bound, the AUC and C_{max} of Zegerid OTC Powder for Oral Suspension is not greater than Prescription Prilosec 40 mg Capsules.

Does the agency agree with this study design?

FDA Preliminary Response:

We agree that a 2-arm study comparing Zegerid OTC Powder for Oral Suspension 20 mg to Prescription Prilosec 40 mg Capsules is acceptable. For this comparative PK study, we recommend that healthy subjects be used. The sample size should be determined based on intra-subject variability of testing products. A single dose study will be acceptable if you have data to support that the percent increase in C_{max} after multiple dosing for Zegerid OTC Powder for Oral Suspension 20 mg is no greater than that for Prescription Prilosec 40 mg Capsules. Otherwise a multiple dose study may be needed.

Additional Discussion for Question 1:

Schering stated they will use a statistically-based sample size for the PK study as suggested, and will submit the final study protocol for Agency review and comment. Schering proposed to do a single dose PK study, as the attached data summary demonstrates that the percent increase in C_{max} after multiple dosing for Zegerid OTC Powder for Oral Suspension 20 mg is lower than that for Prescription Prilosec 40 mg capsules, and these findings are similar for other Zegerid

dosage forms such as the capsules and chewable tablets. FDA replied that a single dose study appears reasonable and requested that Schering submit multiple dosing data for various Zegerid 20 mg and 40 mg dosage forms for our review, to demonstrate consistency. Schering agreed to do so.

3.2 Question 2

There was no request for a Safety Update in the July 12, 2010 Complete Response. The Safety Update submitted in our January 13, 2010 reply to the Agency's January 16, 2009 Complete Response contained the following safety data:

- Safety data from clinical trials conducted with Zegerid since submission of the NDA.
- An update of omeprazole worldwide experience which includes:
 - An update of postmarketing safety data for Zegerid since the last safety update.
 - Analyses of AERS and WHO databases based on line listing information as described in our March 25 submission and confirmed in the Agency response dated April 2, 2009.
 - Updated omeprazole safety information from the DAWN and AAPCC databases.
- An update of medical literature relevant to safety since submission of the last safety update.

As expected for a drug that has a long history of safety, the additional data submitted in numerous safety updates for Zegerid OTC dosage forms has not had any impact on the overall safety profile for omeprazole.

If required, we propose a safety update containing the following elements:

- Safety data from clinical trials conducted with Zegerid since the cut-off date of data provided in the previous safety update.
- An update of omeprazole worldwide experience which includes:
 - An update of postmarketing safety data for Zegerid since the cut-off date of data provided in last safety update.
 - An update of AERS and WHO safety data since the cut-off date of data provided in last safety update.
- An update of medical literature relevant to safety since submission of the last safety update.

Does the Agency concur with this approach?

FDA Preliminary Response:

We are not requiring an additional safety update at this time.

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS:

1. Schering will submit a single dose PK study protocol and the statistical rationale for study sample size for FDA review and comment.
2. Schering will provide multiple dosing PK data for other Zegerid 20 mg and 40 mg dosage forms, including capsules and chewable tablets.

5.0 ATTACHMENTS AND HANDOUTS

Attached is Schering's handout providing multiple dosing data for Zegerid OTC Powder for Oral Suspension 20 mg compared to Prescription Prilosec 40 mg Capsules.

Zegerid Powder - 20 mg^a

	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>
# subjects	35	35	
C _{max} , ng/mL	671.9	902.2	34.28%

Prilosec 40 mg Capsule^b

	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>

# subjects	35	35	
C _{max} , ng/mL	671.9	902.2	34.28%

Prilosec 40 mg Capsule^b

	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>

subjects
C_{max}, ng/mL

32	31	
1040	1677	61.25%

Prilosec 40 mg Capsule^c

	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>

subjects
C_{max}, ng/mL

35	35	
887.5	1344	51.44%

Prilosec 40 mg Capsule^d

	Day 1	Day 7	
	<u>Mean</u>	<u>Mean</u>	<u>% Δ</u>

subjects
C_{max}, ng/mL

35	35	
938	1417	51.07%

Footnotes:

a: data from Santarus Study OSB-IR-C06

b: data from Santarus Study OSB-IR-C02

c: data from Santarus Study OME-IR(CAP)-C02

d: data from Santarus Study OME-IR(TAB)-C02

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22283

GI-1

SCHERING
PLOUGH
HEALTHCARE
PRODUCTS INC

Zegerid OTC (omeprazole 20 mg
& sodium bicarbonate 1680mg)
powder.

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/s/

JOEL SCHIFFENBAUER
09/07/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

E-MAIL TRANSMITTAL SHEET

DATE: June 16, 2010

To: William Cochran	Mary Vienna
Company: Schering Plough Healthcare Products, Inc.	From: Division of Nonprescription Clinical Evaluation
E-mail: william.cochran@spcorp.com	E-mail: mary.vienna@fda.hhs.gov
Phone number: 862-245-5197	Phone number: 301-796-4150

Subject NDA 22-283 labeling comments

:

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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The following comments are in response to your June 11, 2010 submission of revised labeling for NDA 022283 Zegerid™ OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension. These comments are preliminary in nature and should not be considered a complete evaluation of your proposed labeling.

1. For consistency with the labeling of other drugs in this class, remove the periods from the ends of the statements under “Tips for managing heartburn” on the side panel of the carton.

2. In ***Drug Facts*** under ***Warnings, Ask a doctor or pharmacist before use if you are,*** revise the first bullet to read as follows: “warfarin or clopidogrel (blood-thinning medicine)” (i.e., clopidogrel in lower case and medicine without an “s”).

3. In ***Drug Facts*** under ***Other information,*** revise the second and third bullets to remove

(b) (4)

We request the submission of (b) (4) immediate container (powder packet) and cartons for all SKUs as soon as possible.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22283	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680mg) powder.

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/s/

MARY RUSSELL R VIENNA
06/16/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

E-MAIL TRANSMITTAL SHEET

DATE: May 28, 2010

To: William Cochran	Mary Vienna
Company: Schering Plough Healthcare Products, Inc.	From: Division of Nonprescription Clinical Evaluation
E-mail: william.cochran@spcorp.com	E-mail: mary.vienna@fda.hhs.gov
Phone number: 862-245-5197	Phone number: 301-796-4150

Subject NDA 22-283 labeling comments

:

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2080. Thank you.

The following comments are in response to your January 13, 2010 submission of revised labeling for NDA 022283 Zegerid™ OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension. These comments are preliminary in nature and should not be considered a complete evaluation of your proposed labeling.

1. 2-count and 14-count carton: Add an appropriate net quantity statement to the PDP under “14 powder packets”. The net quantity must be expressed as weight in terms of avoirdupois pound and ounce (see 21 CFR 201.62).
2. 2-count carton: Replace (b) (4) on the PDP with “Follow Sample with a 14-Day Course of Treatment”.
3. 2-count and 14-count carton: Under Purpose in Drug Facts, change the first letter of each major word in the sodium bicarbonate purpose statement to lower case except for the first word in the phrase to read as: “Allows absorption of this omeprazole product”.
4. 2-count carton: Under Warnings in Drug Facts, delete the period at the end of the Allergy Alert statement.
5. 2-count and 14-count carton: Under Drug Facts, under the drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” revise the first bullet to read: “(bullet) warfarin or clopidogrel (blood-thinning medicines)” to be consistent with omeprazole class labeling.
6. 14-count carton: Revise the Directions section so that the information under “14-Day Course of Treatment” is contained on the same panel and is not split between panels. In addition, make the arrow directing users to the Drug Facts panel on the bottom of the carton more prominent.
7. 2-count carton: Add the heading “**Drug Facts** (continued)” before the Questions or Comments section on the side panel to be in compliance with 21 CFR 201.66(c)(1).
8. Immediate container (powder packet): We recommend that the net quantity statement be revised to be consistent with the net quantity statement on the PDP.

(b) (4)

We request the submission of revised labeling for the package insert, immediate container (powder packet) and cartons for all SKUs as soon as possible.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22283	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680mg) powder.

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/s/

MARY RUSSELL R VIENNA
05/28/2010



NDA 22-283

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Cochran:

We acknowledge receipt on January 14, 2010 of your January 13, 2010 resubmission to your new drug application for Zegerid™ OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension.

We consider this a complete, class 2 response to our January 16, 2009 action letter. Therefore, the user fee goal date is July 14, 2010.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Mary R. Vienna
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22283	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680mg) powder.

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/s/

MARY RUSSELL R VIENNA
01/28/2010

From: Vienna, Mary R
Sent: Wednesday, October 01, 2008 12:50 PM
To: 'Cochran, William'
Subject: Schering's response to last IR

Hi Bill;

We've reviewed Monday's submission, and unfortunately there are still missing items in the analysis. Below is what we still need by the end of this week. The Santarus analysis will also need to be in this format:

AERS--need total number of cases (patients involved) in database.

Table 1, AERS deaths vs. serious vs. non-serious vs. outcome unknown (add another column # of deaths in database)

- Need total # of deaths, total # of cases with serious outcome, total # with non-serious outcome, total # cases with unknown outcome displayed as the last row
- Calculate % of each outcome/total cases

We are still waiting for their analyses of deaths in AERS.

Table 2, AERS data stratified by dose

- Need total # cases (patients) for 10 mg, 20 mg, 40 mg, 80 mg, other, and unknown displayed as the last row
- Calculate % of cases from each dose/total cases

Table 3, AERS data stratified by age

- Need total # cases (patients) for each age group displayed as the last row in table
- Calculate % of cases from each age group/total cases

Repeat same for WHO exUS and Santarus (which we are still waiting for).

If you'd like to speak with the medical officer for clarification, Christina is willing to discuss this further with you. If you need your analysis person in California or in Schering Plough to speak with us, I can arrange a t-con to do so. Thanks.....Mary

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/s/

Mary R Vienna
12/8/2008 12:41:24 PM
CSO

Hi Bill;

Here are the responses to your questions regarding the safety data.....Mary

FDA: We request submission of the **summary tables** for omeprazole AEs with frequencies **greater than 0.5% of overall AEs** by preferred terms from the Santarus, AERS, WHO databases up to June 21, 2008.

SP: At the time of the submission of the 4-Month Safety Update we only had the data up to June 21, 2008 for the TESS data requested by the Agency. What was available at that time only included data up to December 31, 2007. It is my understanding that these databases are often between 1 and 4 quarters behind in their data entry. We are asking for the most up-to-date data available now. It will take 3 weeks from the request for new WHO or AERS data until receipt of the updated data.

FDA clarification: We are not asking for TESS data. In the interest of time, It is acceptable to provide summary tables for omeprazole AEs frequencies greater than 1.0% of overall AEs from Santarus, AERS and WHO databases up to December 31, 2007.

FDA: We request that the total cases/total adverse events clearly display the following:
One table displaying serious AEs vs. nonserious vs. unknown in both number of reports and % of total from each database.

SP: I want to ensure that the Agency expects one table with 18 columns, e.g.:

WHO		AERS		SNTS							
Unknown	Non-Serious										
n	%	n	%	n	%	n	%	n	%	n	%

FDA clarification: We need three different tables. One for WHO (ex US only), one for AERS, one for SNTS. Each table should have serious vs.. nonserious vs.. unknown in both n and %.

FDA: One table for AEs associated with 20 mg vs. 40 mg vs. 80 mg vs. unknown in both number of reports and % of total from each database.

SP: I want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs.

FDA clarification: Yes. Also, it is acceptable to provide omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: One table of AEs stratified by age from each database.

SP: I want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs..

FDA clarification: Yes. It is acceptable to provide omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: For the WHO database, we request that these tables address both overall and exUS.

SP: Does the Agency want one table that breaks out the global vs. total AEs? I also want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs..

FDA clarification: Please provide one table contrasting total global vs.. exUS AEs. It is acceptable to provide only omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: Please provide a summary and analysis on deaths/serious adverse events by omeprazole dose 20 mg vs. 40 mg for omeprazole postmarketing safety data from FDA/WHO exUS databases (2003-June 13, 2008, encompassing the dates from original submission to the update). Line listing will not suffice.

SP: Is this all deaths/serious adverse events or deaths/serious adverse events occurring with frequency greater than 0.5% of overall AEs? We want to confirm that by "FDA/WHO ex US" in the request above that the Agency wants summary and analysis on one table with data from AERS and WHO exUS broken down by dose and not two tables (one for 20 mg doses and one for 40 mg doses).

FDA clarification: Please clarify how many deaths/serious AEs there were in FDA database and how many deaths/serious AEs there were in WHO exUS. The information should be broken down by dose.

One table for FDA data, one table for WHO data. e.g.:

20 mg 40 mg

Death

SAE

FDA: We also request the study report for IND 74,284 (CL 2008-02, Zegerid OTC capsule PD study) if it is available.

SP: This study report is not yet available.

FDA: That's fine.

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/s/

Mary R Vienna
12/8/2008 12:30:17 PM
CSO

From: Vienna, Mary R
Sent: Monday, September 15, 2008 1:01 PM
To: 'Cochran, William'
Subject: FW: Safety IR for Zegerid NDAs 22-281 & 22-283
Hi Bill;

Per your voicemail, I'm resending the additional IR that I sent last week (see below). In addition, please provide a summary and analysis on deaths/serious adverse events by omeprazole dose 20 mg vs. 40 mg for omeprazole postmarketing safety data from FDA/WHO exUS databases (2003-June 13, 2008, encompassing the dates from original submission to the update). Line listing will not suffice. Thanks so much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

From: Vienna, Mary R
Sent: Tuesday, September 09, 2008 8:26 AM
To: 'Cochran, William'
Subject: Safety IR for Zegerid NDAs 22-281 & 22-283

Hi Bill;

I have an information request for additional safety information to be submitted for NDA 22-281 and 22-283:

We request submission of the summary tables for omeprazole AEs with frequencies **greater than 0.5% of overall AEs** by preferred terms from the Santarus, AERS, WHO databases up to June 21, 2008.

We request that the total cases/total adverse events clearly display the following:

One table displaying serious AEs vs. nonserious vs. unknown in both number of reports and % of total from each database.

One table for AEs associated with 20 mg vs. 40 mg vs. 80 mg vs. unknown in both number of reports and % of total from each database.

One table of AEs stratified by age from each database.

For the WHO database, we request that these tables address both overall and exUS.

We also request the study report for IND 74,284 (CL 2008-02, Zegerid OTC capsule PD study) if it is available.

We need this information ASAP. Please contact me if you have any questions. Thanks so much.....Mary

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/s/

Mary R Vienna
12/8/2008 12:20:13 PM
CSO

From: Vienna, Mary R
Sent: Friday, August 08, 2008 7:31 AM
To: 'Cochran, William'
Subject: Zegerid NDAs safety information request

Hi Bill;

This is the additional safety information request we discussed on the phone.

Schering-Plough mentioned a safety study, OME-IR(SUSP)-C07, which was done at the request of the Division of Gastroenterology Products. FDA requests the full study report of this study. In addition, we request that you submit the full study reports of any available clinical studies conducted with 20 mg and 40 mg Zegerid products.

Thanks.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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10903 New Hampshire Avenue
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/s/

Mary R Vienna
12/8/2008 12:04:42 PM
CSO

From: Vienna, Mary R [mailto:Mary.Vienna@fda.hhs.gov]

Sent: Monday, August 18, 2008 01:32 PM

To: Cochran, William

Subject: FW: NDA 22-283

Hi Bill; We have some missing information from NDA 22-283. Could you please send the Executed Batch record for this NDA? Apparently it was listed in the table of contents but the content was not included in the NDA submission. The CMC reviewer is requesting it. Thanks.....Mary

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/s/

Mary R Vienna
12/8/2008 11:50:29 AM
CSO

From: Vienna, Mary R
Sent: Thursday, July 10, 2008 11:56 AM
To: 'Cochran, William'
Cc: Christl, Leah A

Subject: RE: Paragraph IV Patent Certification Amendment

Bill; We looked into the situation, and the 45-day clock starts the day after the patent holders (including AstraZeneca) receive the notice, not when you submit the return receipts to the FDA (per 314.52(f)). So the 45-day start date is one day after the date of receipt posted on the return receipts. It's Schering-Plough's responsibility to monitor that time and to notify us if any legal action is taken.

314.52(e) requires that we receive documentation of receipt by either return receipt or by a letter acknowledging receipt before we can approve the application. In the case of AstraZeneca, you can either submit the signed receipt when you get it, or you can get a letter from them acknowledging receipt.

I hope you find this helpful.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Wednesday, July 09, 2008 9:48 AM
To: Vienna, Mary R
Subject: Zegerid OTC Capsules and Powder Paragraph IV Notifications
I was wondering if you have had a chance to discuss my Paragraph IV Amendments with Leah.

Was the submission sufficient to start the 45 day clock and if so can you tell me what that start date is?

If it was insufficient, do I need to provide more information about the AstraZeneca US notification?

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Wednesday, July 02, 2008 7:20 PM
To: Vienna, Mary R
Subject: Paragraph IV Patent Certification Amendment

Mary, attached is a copy of one of the Paragraph IV Return Receipts Amendment. I sent desk copies of both Capsule and Powder to you via fed-ex.

I may have made a mistake in this submission in that I stated that "as of today, July 2, 2008" we have received all but one return receipts from the patent holders. Our problem is that AstraZeneca (US) never sent our return receipt back. Included in the submission is a letter from our lawyer explaining what the

US Postal Service gave as a reason that we have not yet received it. Apparently all certified mail goes to AstraZeneca (US) in bulk and Astra's mail room sends the return receipts back when they get around to it. Amongst the other recipients of the notifications is AstraZeneca (Sweden) and we do have confirmation that they received the notifications on June 10th.

We received questions from AstraZeneca's legal council about our applications via a fax on June 19 from their outside legal council to our outside patent legal council. So we know that they received the notification and are aware of it. I did not include that fax in my submission because at the time it didn't seem like any pertinent information. There is nothing in it that we want to hide from the Agency it is a request for DMFs and Drug Manufacturing information, which we are preparing for them.

In my submission I stated that as of today, July 2, 2008 we have received all but one of the return receipts and explained the one that I do not yet have. Should I have stated as of June 19th, we received all but one receipt? I want to make sure that I start the 45 day clock from the right place. Can you give me any guidance?

I do not know why I sent the submission before asking this question. On my train ride home I pondered the situation and realized that I should probably have dated it when we got the fax from AstraZeneca's legal council as that was the last date, rather than "as of today". I apologize for the confusion. 505(b)(2)s are new to me and to Schering.

If I need to send another amendment and include the fax I will gladly do so if that helps. I'm not sure if what I provided is unclear.

<<DOC001.PDF>>

Best Regards,
Bill Cochran
Regulatory Affairs

p: 862.245.5197 | f: 862.245.4041 | william.cochran@spcorp.com

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/s/

Mary R Vienna
12/8/2008 11:38:21 AM
CSO



NDA 22-283

DISCIPLINE REVIEW LETTER

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 19, 2008 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension.

We also refer to your submissions dated May 5, August 19, September 25 and 28, and October 8, 16, 22 and 27, 2008.

Our review of the Clinical Pharmacology and Clinical sections of your submission is complete, and we have identified the following deficiencies:

1. Zegerid® OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension is not bioequivalent to Prilosec OTC (omeprazole magnesium 20 mg) tablet. In particular, the mean C_{max} for Zegerid was approximately 2.7-fold compared to that of Prilosec OTC tablets (90% confidence interval: 220.11% - 335.15%). Further, the upper bound of the 90% confidence interval for the percent mean ratio for AUC (0-inf) was 127.24%, exceeding the bioequivalence limit of 125%.
2. Considering that Zegerid 20 mg powder is more bioavailable than the Prilosec OTC tablet, you have not provided adequate safety data to support this application. The application compares the PK parameters of the Zegerid 20mg powder with those of the prescription 40 mg Prilosec capsule, which has not been approved for OTC use. This cross-study comparison is not valid, as the two formulations were not compared in a single study, and it is conceivable that the C_{max} of Zegerid 20 mg powder may be even higher than that of Prilosec 40 mg capsule. Therefore, one cannot bridge the safety of the Zegerid 20mg capsule to the safety data for either 20mg or 40 mg Prilosec formulations.
3. Furthermore, the application does not present any controlled clinical studies directly comparing 20 mg and 40 mg omeprazole with respect to the safety profile, and the postmarketing information analysis is inadequate to refute the difference in safety

profiles of 20 mg vs. 40 mg. The Adverse Event Reporting System (AERS) data identified a potential safety concern with acute renal failure events, with a higher frequency of acute renal failure associated with the 40 mg dose compared to the 20 mg formulation [REDACTED] (b) (4). The World Health Organization (WHO) Vigibase analysis revealed a higher frequency of thrombocytopenia with the 40 mg dose relative to the 20 mg dose [REDACTED] (b) (4). These findings may warrant further investigation, but the lack of precise dose information in the databases and the uncontrolled, incomplete and voluntary nature of postmarketing reports does not allow for a clear assessment of dose-dependent safety differences.

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 Mary Vienna, Regulatory Project Manager, at 301-796-4150.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Andrea Segal
12/3/2008 07:50:00 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-283

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 19, 2008, received March 20, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (20 mg omeprazole & 1680 mg sodium bicarbonate) powder for oral suspension.

We also refer to your submissions dated April 25, 2008 and May 8, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is January 20, 2009.

During our filing review of your application, we identified the following potential review issues:

1. The application did not contain safety data from the National Poisoning and Exposure Database (TESS) or from the Drug Abuse Warning Network (DAWN) database.
2. The application did not include a comprehensive discussion of the literature related to drug safety for this NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Safety data from the TESS and DAWN databases with the 4-month safety update.

2. Translated labeling for Zegerid products from foreign countries where they are marketed without a prescription and identification of whether the particular labeling is for OTC or pharmacy-only/behind-the-count marketing.
3. A comprehensive discussion of the literature related to drug safety for this NDA.
4. Drug Facts labeling in Word format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application for pediatric patients below 18 years of age. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Joel Schiffenbauer
5/16/2008 08:46:22 AM
for Dr. Leonard-Segal

Vienna, Mary R

From: Vienna, Mary R
Sent: Friday, May 02, 2008 8:04 AM
To: 'Cochran, William'
Cc: Smith, Geri; Chang, Christina; Shetty, Daiva
Subject: RE: NDA 22-281 and 22-283 Action Plan

Bill; We have reviewed the content of your action plan and find it acceptable. Please submit the information by Monday for both NDAs as we discussed - the timing proposed below for submission is not acceptable. Thanks.....Mary

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Thursday, May 01, 2008 1:11 PM
To: Vienna, Mary R
Subject:

Mary, we no longer have the stratification question that I mentioned to you this morning. Here is our action plan in response to your communication Monday.

We will be amending Module 5 to include an ISS for both NDAs.

We will be updating the original summary of safety that was provided in Module 2 to include a separate review and analysis of the postmarketing databases (Santarus, WHO and AERS) stratified as requested where the databases support such stratification.

This will be in addition to the overall analysis and review already included in Module 2 sections 2.7.2 and 2.7.4.

The ISS will include separate sections that include:

- * QT/QTc information
- * A summary of the literature that is available on drug-drug interactions for both omeprazole and sodium bicarbonate
- * We will be making a commitment to provide safety data from the National Poisoning and Exposure Database (TESS) and data from Drug Abuse Warning Network (DAWN).

For the sake of clarity, I want to confirm the location of the ISS in Module 5. You had mentioned in your e-mail on Monday 5.3.6 but the current CTD guideline shows that the ISS should be located in 5.3.5? Will you confirm

You asked for this information by close of business Friday and we are requesting that we be allowed to send this first thing Monday morning instead of close of business Friday. We will provide you first thing Monday morning the text of the ISS for the Capsules NDA (22-281) via e-mail and follow up with a submission with the text, tables, and attachments.

The ISS information that we will be adding for both NDAs is essentially the same. Since the Capsule NDA (22-281) filing date is May 9, and the Powder is 10 days later we propose that we be allowed to provide the Capsule information on Monday and follow up with the official Powder submission by Friday May 9, 2008.

We want to work with the Agency collaboratively to get all of the information necessary to support these NDAs. Please let me know if there is anything that I can provide.

5/2/2008

Best Regards,
Bill Cochran
Regulatory Affairs
Schering-Plough HealthCare Products, Inc.
556 Morris Avenue
S-4-2 Mail Stop 2180
Summit, NJ 07901-1330
T (908) 473-1858
F (908) 473-1741

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/s/

Mary R Vienna
5/2/2008 11:28:28 AM
CSO

Vienna, Mary R

From: Vienna, Mary R
Sent: Tuesday, April 29, 2008 9:33 AM
To: 'Cochran, William'
Cc: Smith, Geri; Chang, Christina; Shetty, Daiva; Schiffenbauer, Joel; Leonard Segal, Andrea; Christl, Leah A
Subject: NDA 22-281 and 22-283
Importance: High

Bill;

Per my voicemail to you this morning, we identified the following deficiency during our preliminary review of your submissions: the Integrated Summary of Safety (ISS) section is not included in Module 5 of either NDA. The ISS must be located in Module 5 (section 5.3.6) of each NDA. The clinical summary in Module 2 does not take the place of the integrated summaries in Module 5. Before we can file each NDA, you must provide an ISS incorporating the following information:

1. Postmarketing adverse event reports collected by Santarus for both 20 mg and 40 mg Zegerid products, accompanied by a safety analysis. Also describe the method/system by which these data are collected.
2. A description of the proarrhythmic potential of this product. Refer to ICH guidance for industry E14 *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.
3. Data and an analysis of drug-drug interactions (for both omeprazole and sodium bicarbonate).
4. Safety data from the National Poisoning and Exposure Database (TESS) as well as data from Drug Abuse Warning Network (DAWN) database. (In this case, it is acceptable to commit to provide information from these two databases with the 4-month safety update.)

Further, the safety information you did include in the original submissions of the NDAs was submitted in tabular form or as line-listings. This is insufficient. All safety databases must be accompanied by an analysis and a summary. All safety analyses should be stratified by chronology, dose, demographics, severity and seriousness, relation to the drug, and drug-drug interactions.

Provide this information by close-of-business Friday, May 2.

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

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/s/

Mary R Vienna
5/2/2008 11:23:21 AM
CSO

Vienna, Mary R

From: cderdocadmin@cder.fda.gov
At: Wednesday, April 30, 2008 1:38 PM
To: Vienna, Mary R
Subject: DFS Email - N 022283 N 000 19-Mar-2008 - Review (noted no comments - NAI)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 022283 N 000 19-Mar-2008	E86	30-Apr-2008	NR

Document Type: Review (noted no comments - NAI)
Submission Description:

Author(s)/Discipline(s)

1. Mike Welch, BIOMETRICS

Signer(s)

1. Mike Welch
No new clinical studies submitted. DB3 statistical review not required.
30-Apr-2008

REQUEST FOR CONSULTATION

(Division/Office):

CDER OSE CONSULTS

FROM: Geri Smith, RPM, ONP/DNCE x62204

DATE
09-Apr-08

IND NO.

NDA NO.
22-281 and 22-283

TYPE OF DOCUMENT
new NDA

DATE OF DOCUMENT
10-Mar-08 (22-281)
19-Mar-08 (22-283)

NAME OF DRUG
Zegerid OTC

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
17-Jun-08

NAME OF FIRM: Schering-Plough

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

COMMENTS/SPECIAL INSTRUCTIONS: ONP received two new NDAs for Zegerid OTC. NDA 22-281 is for the capsule form of the drug; NDA 22-283 is a powder for oral suspension. Both NDAs are being reviewed simultaneously by the same reviewer in each review discipline and will be discussed together at each review cycle meeting.

The DMETS reviewer, when assigned, will be added to all team meetings and labeling meetings. Please attend as warranted.

Please review the trade name proposed in these NDAs.

PDUFA DATE: 09-Jan-09

ATTACHMENTS: Container and Carton Labels

CC: Archival IND/NDA 22-281 and 22-283

HFD-560/Division File

HFD-560/RPM: Geri Smith and Darrell Lyons

HFD-560/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

Geri Smith, x62204

METHOD OF DELIVERY (Check one)

DFS ONLY (labels sent to DMETS on 03-Apr-08 via email)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Geraldine Smith
4/9/2008 02:34:22 PM



NDA 22-283

NDA ACKNOWLEDGMENT

Schering-Plough HealthCare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zegerid® OTC (20 mg omeprazole & 1680 mg sodium bicarbonate)
powder for oral suspension

Date of Application: March 19, 2008

Date of Receipt: March 20, 2008

Our Reference Number: NDA 22-283

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 19, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-

standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl

4/9/2008 04:24:57 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS SCHERING PLOUGH HEALTHCARE PRODUCTS INC William Cochran 556 Morris Ave S4-2, Mailstop 2180 Summit NJ 07901-1330 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22283				
2. TELEPHONE NUMBER 908-4731858	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO 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: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: 21229				
3. PRODUCT NAME Zegerid OTC Powder for Oral Suspension (OMEPRAZOLE / SODIUM BICARBONATE POWDER FOR ORAL SUSPENSION)	6. USER FEE I.D. NUMBER PD3008091				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
OMB Statement: 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: <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td> <td>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.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>William Cochran</i>	TITLE <i>Sr. Manager Regulatory Affairs</i>	DATE <i>14-March-2008</i>			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$589,000.00					
Form FDA 3397 (03/07)					

Close Print Cover sheet



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: William Cochran
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901-1330

Dear Mr. Cochran:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid OTC powder for oral suspension and capsule formulations.

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2007. The purpose of the meeting was to discuss the proposed development program by SPHC in support of the Rx-to-OTC switch of Zegerid powder for oral suspension and capsule formulations, specifically, to obtain further clarification on the pharmacokinetic study comparing Zegerid OTC powder for oral suspension and Prilosec OTC and the proposed labeling for Zegerid OTC.

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

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: October 30, 2007
Meeting Type: B
Meeting Category: Pre-NDA
Application Number: PIND 74,284
Product Name: Zegerid OTC (20 mg omeprazole/sodium bicarbonate) powder for oral suspension
Zegerid OTC (20mg omeprazole/sodium bicarbonate) capsules
Received Briefing Package September 28, 2007
Sponsor Name: Schering-Plough Healthcare Products
Meeting Requestor: William Cochran
Meeting Chair: Andrea Leonard-Segal, M.D.
Meeting Recorder: Keith Olin, R.Ph.
FDA/CDER Attendees:

Division of Nonprescription Clinical Evaluation

Christina Chang, M.D.	Medical Officer
Keith Olin, R.Ph.	Regulatory Project Manager
Joel Schiffenbauer, M.D.	Deputy Director
Andrea Leonard-Segal, M.D.	Director
Laura Shay, RN, MS, C-ANP	Social Science Analyst

Division of Gastroenterology Products

Hugo Gallo-Torres, M.D.	Medical Team Leader
Wen-Yi Gao, M.D.	Medical Officer

Division of Nonprescription Regulation Development

Reynold Tan	IDS Reviewer
Marina Chang, R.Ph.	Team Leader, IDS

OCP/Division of Clinical Pharmacology 3

Tien Mien Chen, Ph.D.	Pharmacology Reviewer
Sue Chih Lee, Ph.D.	Team Leader, Pharmacology

External Attendees:**Schering-Plough Healthcare Products**

John O'Mullane, PhD	Group Vice President
Stephenie Barba	VP, Regulatory Affairs
Dennis Nelson, Ph.D.	VP, Research & Development OTC Medicines
Luis Salmun, MD	Senior Director, Medical and Scientific Affairs
Stephen Neumann	Senior Director Marketing Support Services
Gretchen Trout	Director, Regulatory Policy and Intelligence
Kristie Egstrand	Senior Rx to OTC Switch Marketing Manager
Ajmal Khan	Research Fellow
Bill Cochran	Manager, Regulatory Affairs
Nancy Miller-Rich	Vice President, Business Development

(b) (4)

	Consultant
Thomas Blake	Regulatory Scientist

Santarus, Inc.

Warren E. Hall	Senior Vice President, Product Development and Manufacturing
E. David Ballard II, MD	Vice President, Clinical Research & Medical
Chares H. Davis	Senior Director, Regulatory Affairs

1.0 BACKGROUND

Schering-Plough Healthcare Products (SPHCP) submitted a meeting request to FDA on August 25, 2007 to discuss a single dose PK study comparing Zegerid OTC powder for Oral Suspension to Prilosec OTC and to discuss proposed labeling for their proposed Zegerid OTC formulations. The Zegerid powder and capsule formulations were approved as prescription products under NDA 21-636 and NDA 21-849 respectively, with Santarus, Inc. as the sponsor. SPHCP entered into an agreement with Santarus to develop the Zegerid products for OTC use. SPHCP intends to submit a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the Zegerid products indicated for the nonprescription treatment of frequent heartburn (occurs 2 or more days per week) in adults 18 years of age and older.

2.0 DISCUSSION

On October 29, 2007, FDA sent preliminary responses to SPHCP to address the questions in their September 28, 2007 meeting package. The questions from SPHCP appear below followed by the preliminary FDA responses in italics.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. A summary of the discussion during the meeting follows the questions and preliminary responses.

2.1 Questions and FDA Preliminary Responses

Preliminary Comment:

You provided pharmacokinetic data for the Zegerid 20 mg Powder formulation but not for the Zegerid 20 mg capsule. You need to provide pharmacokinetic data for each Zegerid formulation compared with Prilosec OTC. The data for the powder formulation demonstrates that it is not bioequivalent to Prilosec OTC omeprazole magnesium 20.6 mg, in that the T_{max} is much shorter, C_{max}, and AUC are higher. This generates questions with regard to the safety and efficacy that your program will need to address.

QUESTIONS

Question 1:

Schering intends to submit a NDA for Zegerid OTC under the provisions of section 505(b)(2) of the Act. Does the Agency agree that the sponsor's intention to rely upon safety data contained in the NDA for Prilosec OTC (NDA 21-229) and from studies of Zegerid Rx Powder for Oral Suspension contained in the NDA for Zegerid Rx (NDA 21-636) is sufficient to support the safety of Zegerid OTC in the OTC marketplace and that additional safety studies are not required?

FDA preliminary response:

No. We disagree.

The 20 mg Zegerid powder formulation did not meet the established bioequivalence criteria for C_{max} and AUC. The results of the comparative bioavailability between your proposed OTC Zegerid IR 20 mg powder for oral suspension (Test) and Prilosec OTC 20 mg DR tablet (Reference) showed a more than two fold difference in the mean C_{max} values, the ratio of T/R being 2.20 (90% CI: 271.6 - 335.2). (Table 1, p.11) You should address the safety concerns for this higher C_{max} and AUC. We have previously advised you that appropriate safety data would be needed should Zegerid be shown to be more bioavailability than Prilosec OTC tablets (February 7, 2007 Meeting Minutes & July 18, 2007 Advice Letter).

Based on safety and efficacy, omeprazole magnesium is not approved for OTC consumers at a dose higher than 20.6 mg per day for 14 days. As discussed at the February 7, 2007 meeting, you could provide the safety data from your current prescription omeprazole 40 mg product to help support the safety of your Zegerid 20 mg powder formulation but you would need to compare and contrast those data with the safety data from omeprazole 20 mg.

In addition, since the Zegerid 20 mg powder formulation is more bioavailable than Prilosec OTC tablets, you would need to address the safety of the increased exposure of your 20 mg omeprazole in the Asian population (see the last labeling comment). The same will be true if the Zegerid 20 mg capsule formulation is more bioavailable than Prilosec OTC.

Also, you only provided one single-dose comparative bioavailability study for your proposed OTC Zegerid 20 mg powder for oral suspension. However, you are seeking OTC switch for both Zegerid IR 20 mg powder for oral suspension and Zegerid IR 20 mg capsule. In this case, the comparability between the proposed OTC Zegerid IR 20 mg capsule (Test) and Prilosec OTC 20 mg DR tablet (Reference) will need to be addressed.

Question 2:

Does the Agency concur that the data presented demonstrate that consumers do in fact understand the purpose of sodium bicarbonate in the formula and further that its presence does not deter from proper use of the product as directed? Further, does the Agency concur that no further label comprehension studies are needed?

FDA preliminary response:

A review of your label comprehension study results will be conducted when your NDA is submitted; whether or not additional label comprehension studies will be needed is ultimately a review issue.

Based on the summary of the study results you provided in the meeting background package, it is unclear why you are proposing to use the language [REDACTED] (b) (4) to describe the purpose of sodium bicarbonate (general population 63%, low literate population 56%). As stated in the July 18, 2007 Advice Letter, the "Purpose" section of Drug Facts should clearly describe the effect sodium bicarbonate has on omeprazole (e.g. "to assist in the absorption of omeprazole") and consumers should understand this purpose. In addition, the word [REDACTED] (b) (4) may imply an added benefit. A targeted label comprehension study focusing on consumer understanding of the purpose of sodium bicarbonate for this product should be conducted. Comprehension of the directions for use of the powdered form, specifically mixing it with 2 tablespoons of water and not mixing it with liquids other than water, should also be tested.

We encourage you to submit your proposed study for our review and comment prior to initiating your study.

Question 3:

Does the Agency agree with the proposed labeling for Zegerid OTC with regard to the sodium bicarbonate content?

FDA preliminary response:

This will be a review issue when you submit your application.

The exact purpose of sodium bicarbonate in the label would depend on the result of an appropriately conducted label comprehension study.

You have not adequately addressed our labeling recommendations in Comment 7 of the July 18, 2007 Advice Letter. The warning statement "Ask a doctor before use if you have a sodium-restricted diet" does not adequately address our safety concern regarding bicarbonate-related metabolic disorders, nor does it address the prescription label's precaution regarding acid-base disorders. We do not agree that your proposed OTC warnings and directions statements communicate the same information as warnings in the current prescription labeling. As we stated in Comment 7, safety issues in the current prescription labeling need to be addressed in the OTC label. You should provide additional justification as to why you believe that some of the warnings from the prescription label are not needed in the OTC label.

Under "Ask a doctor or pharmacist before use if you are", you should include the following statements:

Presently taking any prescription drug(s) or taking any of the following:

Warfarin (blood-thinning medicine)

Prescription antifungal or anti-yeast medicines

Diazepam (anxiety medicine)

Digoxin (heart medicine)

Atazanavir (anti-viral medicine)

Under "Directions" for the Zegerid OTC powder, a statement is needed to specify that the product should be taken before eating in the morning. Such a statement already appears in directions for the Zegerid OTC capsule. The need for further revisions to improve the clarity of directions will be a review issue.

Under "Ask a doctor before use if you have", the statement "liver and/or kidney disease" should be included.

You need to include appropriate warnings to address the issue of a four-fold increase in AUC from Zegerid 20 mg powder in the Asian population, or provide justification as to why such warnings are not needed. The new warning may require comprehension testing.

2.2 ADDITIONAL DISCUSSION

Schering-Plough Healthcare Products (SPHCP) opened the meeting by acknowledging the FDA preliminary comments sent to them. SPHCP noted that the PK data for the capsule is not available at this time but they committed to provide PK data for each Zegerid formulation compared with Prilosec OTC. SPHCP acknowledged that the bioavailability of the omeprazole in the Zegerid powder formulation is higher than the bioavailability of the omeprazole in Prilosec OTC. FDA clarified the preliminary comment stating that SPHCP will need to justify both the safety and efficacy of the powder formulation since it showed a higher C_{max}, a higher AUC, and a shorter T_{max} compared to Prilosec OTC. Regarding efficacy, FDA explained that based on the data provided, it is possible that there is a dip in the Zegerid powder omeprazole bioavailability late in the dosing interval when compared with Prilosec OTC. If this is the case, then during this time efficacy may be compromised. FDA asked if Zegerid OTC's PK and PD profile impacted efficacy and time to onset compared to Prilosec OTC. FDA asked SPHCP to also explain how the PD data (meaning pH data) is converted to PK data. Also, FDA commented that there is not a good correlation between PK and PD and clinical efficacy, and that SPHCP will need to address these concerns by building a bridge to efficacy. To address safety concerns generated by increased bioavailability, SPHCP should also perform an analysis of adverse events from 2003 to 2007 comparing Prilosec OTC, omeprazole 40 mg and Zegerid 20 mg and 40 mg formulations. FDA agreed to SPHCP's request for a teleconference to be scheduled to discuss their rationale for bridging PK data to Zegerid OTC efficacy.

SPHCP then moved to address the FDA preliminary responses. SPHCP had a question regarding the statement in paragraph 3 of the response to Question 1, which referred to the Asian population warning. FDA clarified that Zegerid 20 mg powder has a higher C_{max} and that 40 mg Prilosec has this warning in its label. SPHCP stated they did not believe the higher C_{max} posed a safety concern for Asians because Asians had a higher elimination rate. FDA informed SPHCP they would need to provide a rationale for why a warning for the Asian population would not be needed for the OTC Zegerid product. This rationale could be in the form of medical literature demonstrating that the increased AUC would not be a safety concern in the Asian population.

Next SPHCP asked FDA to clarify their preliminary response to Question 2. FDA reiterated that the data from the label comprehension study provided was not reviewed. Analysis of this data will only be conducted when the study is submitted in support of the new drug application. SPHCP acknowledged this. FDA stated that based on the summary results provided, SPHCP should conduct a targeted label comprehension study

that focuses on the new language describing the purpose of sodium bicarbonate and directions for use. SPHCP stated that they tested several terms to describe the purpose of sodium bicarbonate in their product, such as (b) (4) (b) (4) but they would consider other terms. They acknowledged FDA's recommendation to test the comprehension of the directions for use of the powder and said they would consider doing this. FDA suggested that SPHCP submit a protocol for FDA review and comment prior to conducting any study.

Regarding the preliminary response to Question 3, SPHCP asked why Zegerid should have additional labeled warnings addressing sodium bicarbonate-related metabolic disorders or acid-base disorders. SPHCP commented that AE's related to metabolic disorders were not seen in clinical trials and post-marketing reports and therefore they did not feel that wording related to metabolic disorders was needed. SPCHP also questioned the need for a sodium warning because there are products in the monograph with higher amounts of sodium that do not have all of these warnings. FDA suggested that SPHCP submit their rationale on why the sodium bicarbonate warnings should not be translated from the prescription Zegerid to the OTC formulations. FDA also recommended the same advice regarding the liver warning. SPHCP should include safety data concerning chronic exposure, including adverse events in individuals with liver and/ or kidney disease.

SPHCP commented that they will be including a statement in the label under the "Directions" section that the product should be taken before eating in the morning.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Neither FDA nor SPHCP identified any issues requiring further discussion.

4.0 ACTION ITEMS

- 1) SPHCP will provide a rationale to address the concern that differences in PK will translate into differences in efficacy when compared to Prilosec OTC. They will provide data to allow bridging of PK data to efficacy. SPHCP will submit this information to the FDA along with a request for a teleconference.
- 2) SPHCP will provide a rationale to the FDA addressing the warnings related to the Asian population.
- 3) SPHCP will provide a label comprehension study protocol to the FDA for review.
- 4) SPHCP will submit their rationale as to why the sodium bicarbonate warnings should not be translated from the Rx Zegerid to the OTC formulations.

5.0 ATTACHMENTS AND HANDOUTS

None

Linked Applications

Sponsor Name

Drug Name

IND 74284

SCHERING-PLOUGH
HEAL

ZEGERID IR

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/s/

KEITH J OLIN

11/29/2007

ANDREA LEONARD SEGAL

11/29/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: John O'Mullane, Ph.D.
Group Vice President
556 Morris Avenue
Summit, NJ 07901-1330

Dear Dr. O'Mullane:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid (20mg omeprazole and sodium bicarbonate) capsule and powder for oral suspension.

We also refer to your correspondence dated March 21, 2007 explaining how your development plan for Zegerid for OTC use will meet the fixed-combination drug requirements in 21 CFR 300.50.

We have completed the review of your submission and have the following comments.

1. We agree that the purpose of the sodium bicarbonate in your product is (b) (4) the absorption of omeprazole and will have no direct impact on providing heartburn symptom relief. To gain approval for Zegerid for the OTC treatment of frequent heartburn, you will need to provide a pharmacokinetic (pK) study that compares the bioavailability of your product to Prilosec OTC, the reference listed drug for the OTC indication. If the pK parameters fall outside of the bioequivalence criteria established by FDA for oral drugs, you will need to provide additional data to support the efficacy or safety of your product. This may require a clinical study depending what the difference entails. For example, if your product is less bioavailable than Prilosec OTC, you will have to provide clinical efficacy data to support the efficacy of your drug product.
2. If you are successful in bridging your product to Prilosec OTC through pK data, such data will not support a claim in labeling or advertising suggesting that your product is better than Prilosec OTC. Additionally, labeling implying an immediate effect will not be acceptable based on such data.
3. The sodium bicarbonate is an active ingredient and should be listed in the active ingredient section of the Drug Facts label. Because it is not intended to have a direct impact on providing heartburn relief, the purpose should not be listed as (b) (4) but as something such as "to assist in the absorption of omeprazole".
4. To assure that consumers will not be confused about the use of this product and the function of the sodium bicarbonate, you may be required to provide a label

comprehension study and possibly consumer behavior studies that demonstrate consumers will use the product correctly.

5. The product should contain sodium labeling if it falls within the criteria listed in 21 CFR 201.64.
6. Because consumers will be exposed to a daily dose of sodium bicarbonate, you will need to include any warnings that are applicable to sodium bicarbonate.
7. Because this product is a fixed-dose combination containing both omeprazole and sodium bicarbonate, it may present different safety issues when used OTC compared to single ingredient omeprazole. For example, the current labeling for prescription Zegerid includes contraindications in patients with metabolic alkalosis and hypocalcemia and cautions about use in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. These warnings are not applicable to single ingredient omeprazole. You will need to identify any potential safety issues included in the current prescription labeling or new safety issues after review of your safety database and determine how they should be addressed with OTC marketing. Despite being labeled for use for a fourteen day regimen, some people may use it longer than directed if it is available OTC. This should be factored into the considerations when attempting to address safety issues.

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at 301-796-0962.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Charles Ganley
7/18/2007 04:33:34 PM

Telecon Minutes Memo

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products

Date: 4-25-07

Participants: John O'Mullane, Ph.D., Schering-Plough HealthCare Products
Charles Ganley, M.D.

Discussion Issues: Clinical requirements for Zegerid (PIND #74-284); information amendment dated

- We met with John Jenkins and the lawyers from CDER Office of Regulatory Policy and FDA Office of Chief Counsel.
- There is a letter in draft that probably will not be cleared for another month.
- The preliminary decision is:
 - A bridging pharmacokinetic study would suffice if bioequivalence criteria are met. If the bioequivalence criteria are not met, they would have to provide additional information to support the efficacy and/or safety. This may include additional clinical studies depending on what the data shows.
 - Sodium bicarbonate is an active ingredient but the purpose is not as an ^{(b) (4)} It would be described something such as "adjuvant to assist the absorption of omeprazole".
 - There are several other caveats alluded to but not discussed.

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/s/

Charles Ganley
5/2/2007 12:07:50 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: William Cochran
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901-1330

Dear Mr. Cochran:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid immediate release powder for oral suspension and capsule formulations.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss the proposed development program by Schering-Plough HealthCare Products (SPHC) in support of the Rx-to-OTC switch of Zegerid immediate release powder for oral suspension and capsule formulations, specifically, that the comparative bioavailability study meets the criteria for approval and to gain agreement on the elements and design of the labeling for Zegerid.

The official minutes of that meeting were signed off by the FDA on March 9, 2007. At the time of the meeting, there was an outstanding item that required follow-up by SPHC to submitted additional chemistry stability data. SPHC felt that there was an agreement in regards to the chemistry stability data which was discussed at the meeting on October 26, 2005. SPHC submitted the requested information as an amendment on March 10, 2007.

Enclosed is a revised copy of the March 9, 2007 meeting minutes edited to correct minor typographical errors and to include a post-meeting addendum to the minutes addressing the outstanding issue described above in reference to Question 3.

This letter and the enclosed meeting minutes represent the official record of the meeting on February 7, 2007.

If you have any questions, call LCDR Keith Olin Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division on Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research



FOOD AND DRUG ADMINISTRATION

Meeting Date: February 7, 2007

Meeting Type: B

Meeting Category: pre-IND

Meeting Location: FDA/White Oak
10903 New Hampshire Ave
Room 1415
Silver Spring, MD 20993

Application Number: PIND 74,284

Product Name: Zegerid omeprazole/sodium bicarbonate
immediate release powder for oral suspension(20mg
omeprazole)
Zegerid omeprazole/sodium bicarbonate immediate
release capsules

Received Briefing Package January 8, 2007

Sponsor Name: Schering-Plough Healthcare Products

Meeting Requestor: William Cochran
Manager, Regulatory Affairs

Meeting Chair: Andrea Leonard-Segal, M.D., Director

Meeting Recorders: Keith Olin, R.Ph., Regulatory Project Manager

FDA/CDER Attendees:

Office of Nonprescription Products (ONP)
Charles Ganley, M.D. Director

ONP/Division of Nonprescription Clinical Evaluation
Leah Christl, Ph.D. Chief, Project Management Staff
Wafa Harrouk, Ph.D. Pharmacology/Toxicology Reviewer
Andrea Leonard-Segal, M.D. Director
Bindi Nikhar, M.D. Medical Team Leader
Keith Olin, R.Ph. Regulatory Project Manager
Linda Hu, M.D. Medical Officer
Joel Schiffenbauer, M.D. Deputy Director
Daiva Shetty, M.D. Medical Team Leader

ONP/Division of Nonprescription Regulation Development

Helen Cothran IDS Team Leader

Reynold Tan, Ph.D. IDS Reviewer

Division of Gastroenterology Products

Joyce Korvick, M.D. Deputy Director

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Michael Welch, Ph.D. Statistician Team Leader

Division of Clinical Pharmacology 2

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Lei K. Zhang Senior Staff Fellow

Division of Pre-Marketing Assessment II

Shulin Ding, Ph.D. Lead Chemist

Division of Pharmacology III

Tien-Mien Chen, Ph.D.

External Attendees:Schering-Plough Healthcare Products

John O'Mullane, PhD Group Vice President

Luis Salmun, MD Senior Director, Medical and Scientific Affairs

Robert Nowak, PhD Director, Clinical Research

Ajmal Khan Research Fellow

Bill Cochran Manager, Regulatory Affairs

Nancy Miller-rich Vice President, Business Development

(b) (4)

Consultant

Thomas Blake Regulatory Scientist

Santarus, Inc.

Warren E. Hall Senior Vice President, Product Development and Manufacturing

E. David Ballard II, MD Vice President, Clinical Research & Medical

1.0 BACKGROUND

Schering-Plough HealthCare Products (SPHC) submitted a pre-IND meeting request on November 22, 2006, received on November 27, 2006, to discuss a regulatory approach for an prescription-to-over-the-counter (Rx-to-OTC) switch for Zegerid immediate release powder for oral suspension and capsule formulations. The Zegerid powder and capsule formulations were approved as prescription products under NDA 21636 and NDA 21849 respectively, with Santarus, Inc. as the sponsor. SPHC entered into an agreement with Santarus to develop the Zegerid products for OTC use. According to the January 5, 2007 meeting package, SPHC intends to submit a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the two Zegerid products indicated for the treatment of frequent heartburn (occurs 2 or more days per week) in adults 18 years of age and older.

FDA met with Santarus, Inc. on October 26, 2005 to discuss the Rx-to-OTC switch of Zegerid powder, capsule (b)(4). The meeting minutes for the October 26, 2005 between Santarus and the FDA were issued on November 22, 2005. During the meeting on October 26, 2005, the issue of the applicability of the combination policy for Zegerid as a OTC drug product as per 21 CFR 330.10, subpart B(4)(iv) was not address but a response to this was issued on January 30, 2007. It was determined that the Zegerid products contain two active ingredients, omeprazole and sodium bicarbonate, each of which are available in nonprescription drug products for heartburn indications. Santarus was informed that they would have to satisfy the combination policy by conducting two clinical superiority studies that demonstrate the efficacy and safety of the Zegerid products as nonprescription products to treat frequent heartburn.

Prior to the February 8, 2007 meeting, FDA verified that Santarus had shared the FDA's comments and recommendation with SPHC.

2.0 MEETING OBJECTIVE

The objective of the meeting was to discuss the proposed development program by SPHC in support of the Rx-to-OTC switch of Zegerid immediate release powder for oral suspension and capsule formulations, specifically, that the comparative bioavailability study meets the criteria for approval and to gain agreement on the elements and design of the labeling for Zegerid.

3.0 DISCUSSION

Preliminary responses to the questions enclosed in the January 5, 2007, meeting package were sent to SPHC via e-mail on February 6, 2007. These questions and preliminary FDA responses are listed below.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA.

3.1 FDA Preliminary Responses

3.1.1 Chemistry

The Chemistry, Manufacturing and Controls for the OTC forms of Zegerid®, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) will be virtually identical to those for the prescription products, with the slight exception that tamper evident banding will be applied to the capsules, as per 21 CFR 211.132. Thus, Schering-Plough will reference the currently approved NDAs for Zegerid, including existing stability and expiry dating, in its application for the OTC version.

20 mg Powder for Oral Suspension

1. Because the container-closure will not change, does FDA agree that the current expiry dating for Zegerid Powder can be applied to the OTC version?

FDA Preliminary Response:

Yes, it can be applied if the CMC package of the OTC version is identical to the prescription Zegerid as you stated in the briefing package. If there are differences in CMC between OTC and prescription Zegerid, the actual expiry period granted is a review issue.

20 mg Capsule

The following changes to the capsule are anticipated to accommodate the OTC indication (see Exhibit 8.2.1 for more details):

The capsule shell will be all white (Deletion of FD&C Blue #1 and FD&C Red #3 in the capsule shell) as opposed to the half blue/half white color of the Rx product. The capsule imprint graphic will change but the qualitative composition of the imprinting ink will not. A tamper evident band ((b) (4) Gelatin using same FD&C Blue #1 dye as is found in the Rx capsule shell) will be added to the capsule as per the requirements of 21 CFR 211.132. The tamper evident band is on the outside of the capsule shell and will not be in contact with the capsule contents.

A tamper evident feature will also be added to the bottles.

2. We intend to use the current Rx marketed product (blue/white capsule without tamper evident band) in the proposed comparative bioavailability study for the 20 mg capsule product? We plan to demonstrate that the banded capsule meets the current approved dissolution specification for the unbanded capsule. Does the Agency agree with this approach?

FDA Preliminary Response:

The approach appears acceptable provided that 1) virtually, no changes are made to omeprazole drug substance and/or no higher than level 1 changes to the manufacturing site/processes of the proposed omeprazole OTC IR 20 mg capsules other than for coloring agents and packaging of the final OTC IR 20 mg products and 2) dissolution testing meets the currently approved dissolution specification and shows similar dissolution profiles between the currently marketed Zegerid 20 mg IR capsules and the proposed OTC omeprazole IR 20 mg capsules.

3. Schering-Plough will commit to placing the first three commercial lots of 20 mg OTC capsules on stability post-approval (as will be outlined in the stability commitment submitted in the OTC NDA). Would the Agency agree that the changes bulleted above to the capsule would not require generation of pre-market stability data based on full cross-reference being granted to the Rx NDA and stability data contained therein. Would the Agency agree that the OTC NDAs (with changes as summarized above) could be granted approval of the Rx approved expiry dating based on the aforementioned proposal?

FDA Preliminary Response:

No, we disagree. Pre-market stability data will be required for the OTC NDAs on capsules because of the changes outlined on page 49 of the briefing package. The actual expiry period granted is a review issue.

3.1.2 Clinical/Safety Evaluation

4. Schering-Plough proposes to submit New Drug Applications under the provisions of section 505(b)(2) of the Food, Drug, and Cosmetic Act for the OTC marketing of Zegerid, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) in Capsule and Powder for Oral Suspension dosage forms. The prescription equivalents were approved by the Agency in NDAs 21-636 (Powder for Oral Suspension) and 21-849 (Capsule), sponsored by Santarus, Inc. of San Diego, CA. Using a comparative bioavailability study, discussed below, Schering-Plough proposes to compare Zegerid, immediate release omeprazole 20 mg and sodium bicarbonate, with Prilosec OTC 20mg (NDA 21-229). Accordingly, Schering-Plough intends to rely on the Agency's findings of safety, efficacy, and approvability for Prilosec OTC in order to support the NDA submission for Zegerid. Does the Agency agree that a 505(b)(2) application, supported by the data from the comparative bioavailability study outlined in Question 2 fulfills the requirements for approval?

FDA Preliminary Response:

A comparative bioavailability study would support a 505(b)(2) application, but additional data are needed (see below).

5. Schering-Plough's proposal for equivalence of each of the Zegerid dosage forms with Prilosec OTC will be based on a single dose pharmacokinetic study as per the attached protocol synopses (See Exhibits 8.1.1 and 8.1.2). The primary outcome measure will be bioequivalence to Prilosec OTC with respect to AUC. From a safety standpoint, FDA relied upon AUC when it approved Prilosec OTC tablets, since the drug's C_{max} was shown to be significantly higher than that for Prilosec Capsules, the prescription form of the drug. The relevant portion of the Summary Basis of Approval (SBA) for Prilosec OTC (NDA 21-299) is attached for reference (See Exhibit 8.1.3). Also, the single dose design is the basis by which the Office of Generic Drugs evaluates bioequivalence for the generic forms of omeprazole 20mg, as illustrated by a description of the (b) (4) Study No. 97273 in the SBA for ANDA 75-247 Is the Agency in agreement with this approach?

FDA Preliminary Response:

It should be noted that the word, "bioequivalence (BE)", is reserved only when the Agency's acceptance criteria for BE are met, i.e., the 90% confidence intervals of the ratio of least-square means for both $AUC_{(0-inf)}$ and C_{max} fall within 80-125%. Therefore, as stated in the proposed protocols, 90% confidence intervals should be calculated for the ratio of least-square means for both $AUC_{(0-inf)}$ and C_{max} of currently marketed Zegerid to omeprazole OTC 20 mg capsules.

In addition, it should be noted that post-marketing safety data, clinical trial safety and efficacy data and consumer study data were also submitted to support the Prilosec OTC switch. It would be erroneous to suggest that the safety of Prilosec OTC was based only on a pharmacokinetic comparison to the prescription omeprazole product.

Observed differences in the bioavailability of Zegerid and Prilosec OTC would need to be justified or supported by appropriate safety and/or efficacy data. If Zegerid is more bioavailable than Prilosec OTC, more safety information would be needed. If your product is less bioavailable, efficacy data would be needed.

Your product contains two active ingredients, omeprazole and sodium bicarbonate. Omeprazole magnesium is an approved nonprescription drug to treat heartburn and sodium bicarbonate a nonprescription ingredient generally recognized as safe and effective to relieve heartburn. Therefore, even if the omeprazole component of your product proves to be bioequivalent to Prilosec OTC this will be insufficient to support the prescription to OTC switch of Zegerid. You will need to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv). This may be achieved by conducting two clinical studies that demonstrate the contribution of each active ingredient to the efficacy of Zegerid to treat frequent heartburn.

6. Since Zegerid, like Prilosec OTC, will be taken on an empty stomach, the studies will be conducted in the fasting state only. Is the Agency in agreement with this approach?

*FDA Preliminary Response:
The approach appears acceptable.*

7. The Agency did not require or recommend additional safety studies as a condition for approval of the Zegerid 20 mg Rx NDAs'. As these NDAs were 505(b)(2) applications, Santarus referenced several NDAs for omeprazole, particularly those for Prilosec (NDA 19-810) for the safety portions. Does the Agency agree that no additional safety studies will be required for Zegerid, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) if, 1) its bioavailability profile is comparable to that of Prilosec OTC (omeprazole 20 mg), especially with respect to AUC, or 2) if Zegerid's profile is unexpectedly higher, that concerns about safety are adequately addressed by the safety database for omeprazole 40 mg, the highest strength of the prescription drug?

*FDA Preliminary Response:
If Zegerid is not bioequivalent to Prilosec OTC, but its PK profile is unexpectedly higher (for example, higher Cmax), then additional safety data would be needed. Omeprazole 40 mg is not approved for OTC use.*

3.1.3 Regulatory/Procedural

The sponsor of the NDAs for the prescription forms of Zegerid, Santarus granted Schering-Plough a full right of reference to its NDAs in order to facilitate our program for gaining OTC status for the drug.

8. Schering-Plough plans to submit the comparative bioavailability study information to the newly created file, IND 74,284, with appropriate references to the INDs and NDAs for the currently approved Zegerid products. Since the single dose of Zegerid 20mg to be given in the comparative bioavailability study falls well within the drug's margin of safety and is covered by its approved labeling. Please confirm that the standard 30-day IND hold will not apply.

*FDA Preliminary Response:
The standard 30-day IND hold would not apply if you can provide evidence that this product is the same as the approved prescription Zegerid product.*

3.1.4 Labeling

9. As with other OTC acid reducer drugs, we will likely distinguish Zegerid®, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) from its prescription counterpart

(b) (4)

(b) (4)

FDA Preliminary Response:

(b) (4)

10. In view of Prilosec OTC's marketing history and the information in its NDA, does FDA agree that additional labeling comprehension and actual use studies are unnecessary?

FDA Preliminary Response:

Since your product contains two active ingredients, omeprazole and sodium bicarbonate, each of which is an approved nonprescription drug for heartburn, additional clinical studies that demonstrate the contribution of each ingredient to the efficacy of Zegerid to treat frequent heartburn are needed. Final labeling will depend on the results of these trials. If the labeling is substantially different from that of Prilosec OTC, then consumer comprehension (and/or behavior studies) may be needed. It is premature to discuss whether additional label comprehension and actual use trials are needed at this time.

3.1.5 Additional Comment:

Each 14 day course of your product should be packaged separately to further emphasize that 14 tablets constitute one course of therapy to treat frequent heartburn.

3.1.6 Additional Administrative Comments:

Comments shared today with you are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate the meeting discussion. As this meeting is a Pre-IND meeting, the comments from the Agency serve as guidance to you at

this preliminary stage. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the IND might identify additional comments or informational requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We encourage you to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

Your pre-IND has been assigned 74,284. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

When you submit you Investigational New Drug Application, please provide 6 copies.

3.2 Additional Discussion

SPHC opened the meeting with a review of the history of the development of the Zegerid products as prescription products and provided an argument to support why they should not have to conduct clinical trials for their proposed OTC products. The Division of Gastrointestinal Drug Products reviewed data for the prescription application that they felt fulfilled the combination policy for the indication being sought.

FDA responded that for the OTC indication, there are several other factors in the regulatory history that are important when determining what studies may be needed to support an OTC indication of frequent heartburn. They are as follows:

- Sodium bicarbonate is an active ingredient in the OTC drug monograph for the indication of relief of heartburn. From a regulatory perspective, it is no less of an active ingredient than an H2 blocker for this claim.
- In the past, FDA determined that the combination of an antacid and H2 blocker was acceptable for a claim of relief of heartburn. Companies would have to demonstrate

the contribution of each ingredient. For the combination of famotidine and an antacid, the sponsor was required to conduct clinical studies that demonstrated the contribution of each ingredient. (b) (4)

- FDA can not view sodium bicarbonate any differently than other active ingredients for heartburn relief, such as famotidine or ranitidine. So, if a company wanted to come in for a combination of an H2 blocker and omeprazole, FDA would expect them to fulfill the combination policy and conduct clinical trials that demonstrate the contribution of each ingredient.
- If FDA allowed a claim for frequent heartburn Zegerid without conducting clinical trials. (b) (4)

(b) (4) When Prilosec OTC was being developed, multiple studies were conducted to evaluate the effect for the relief of heartburn. None of these studies demonstrated a benefit. If however, omeprazole was combined with an antacid, it may be possible to show a treatment effect in part because of the antacid. FDA has to be consistent with how it deals with combinations such as that proposed for all of the OTC heartburn indications.

- (b) (4)

FDA reiterated to SPHC that the Zegerid formulation is a combination product and will have to follow the combination policy. The FDA stated that they understood that SPHC is using the sodium bicarbonate to protect the omeprazole from stomach acid degradation. If they combined an H2 blocker with omeprazole instead of the antacid, we would expect them to fulfill the combination policy and conduct two clinical studies. FDA explained that there is a regulatory history that needs to be considered and that SPHC's formulation can be compared to other products on the market like a famotidine and antacid combination, which was required to follow the combination policy by demonstrating the contribution of each ingredient. FDA determines what types of trials would be acceptable.

SPHC stated that they agree that the product is a combination drug, but that they felt that they were being held to a different standard with trying to switch the Zegerid product to the OTC marketplace. FDA explained that the reviewing divisions within the Office of New Drugs what information is needed to fulfill the combination policy which is based on different factors such as the indication, the class of drug and previous regulatory precedent. The review divisions have the discretion of deciding what information may be needed for the required studies to comply with the combination policy.

FDA stated that it understands that the sodium bicarbonate is included in Zegerid because of formulation issues, but explained that SPHC has the option of reformulating, as others have done, instead of combining another active ingredient to take care of the problem. FDA explained that the difficulty here is that SPHC is seeking a heartburn indication by combining two drugs that have heartburn indications on their own. In addition, FDA has permitted combinations of two different drugs to treat heartburn, one of them an antacid, and required that the clinical contribution of each ingredient be established through clinical studies.

SPHC noted that if they conducted a factorial study with their product, the individual components and placebo, that the arm with “naked” omeprazole would show no benefit because it would be destroyed by stomach acid. SPHC was told they would likely have to include an omeprazole formulation that demonstrated a clinical benefit superior than placebo. FDA stated that they generally do not accept a factorial study as valid if one of the single ingredient active arms includes a formulation of an active ingredient that is not effective. Also, this combination would also raise issues about whether it is rational to combine these ingredients for a frequent heartburn indication. In the past, FDA determined that the combination of an antacid and an H2 blocker was not rational for a prevention of meal induced heartburn claim. FDA stated that SPHC would need to provide support that this formulation is a rational combination for the indication sought. FDA stated that they had concerns regarding chronic use of omeprazole that SPHC would also have to address.

With regard to relying on the safety database for omeprazole 40 mg to support the safety of the Zegerid products (refer to Question 7), FDA explained that SPHC could provide the safety data from their current 40 mg prescription omeprazole product but that SPHC would need to compare and contrast the data with omeprazole 20 mg.

FDA encouraged SPHC to provide a written response to FDA outlining their argument as to why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv) with clinical studies. FDA stated that they would expedite a response to SPHC.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

SPHC/Santarus felt that an agreement to question 3 in regards to submitting the stability data was made at the first meeting in October 26, 2005 when Santarus met with the FDA and that the response that FDA provided for the February 8, 2007 meeting was different than the meeting minutes from the October 2005 meeting. Below is the response by the FDA given at the October 2005 meeting:

(October 2005) Question 5.

Does the Agency agree that Santarus can rely on the stability data generated for Zegerid 20-mg Rx capsules (packaged in bottles of 5 and 30) to support Zegerid OTC 20-mg

capsules (packaged in identical bottles of 14 and 28) and therefore, no additional stability studies are required?

FDA Response:

This proposal appears to be acceptable. See response to Question 6 below. It should be noted that NDA 21-849 is still under review.



5.0 ACTION ITEMS

1. SPHC will provide the FDA with a written response about why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv).
2. FDA agreed to expedite the review SPHC's response.
3. FDA will follow-up on the stability issue and possible agreement made in October 2005.

6.0 ATTACHMENTS AND HANDOUTS

None

7.0 POST_MEETING ADDENDUM

SPHC submitted an amendment to their meeting package on March 10, 2007 that included the data that the FDA requested at the February 7, 2007 meeting. The submission included a summary of the bracketing approach for package sizes from 5 capsules to 30 capsules and a table summarizing the bottle dimensions, including headspace.

The FDA agrees with SPHC's proposal submitted on March 10, 2007, for the additional supporting chemistry data regarding headspace, surface area, and volume for the bottles used in the prescription NDA and the proposed OTC product. The FDA also agrees that the information provided in the amendment shows that the OTC packaging configurations of 14 and 28 counts are bracket by the approved prescription configurations of 5 and 30 counts. This information should be included in any NDA submission as justification.

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

/s/

Andrea Segal
5/1/2007 11:25:47 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: William Cochran
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901-1330

Dear Mr. Cochran:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid immediate release powder for oral suspension and capsule formulations.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss the proposed development program by SPHC in support of the Rx-to-OTC switch of Zegerid immediate release powder for oral suspension and capsule formulations, specifically, that the comparative bioavailability study meets the criteria for approval and to gain agreement on the elements and design of the labeling for Zegerid.

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

If you have any questions, call LCDR Keith Olin Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Charles Ganley, MD
Director
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

Meeting Date: February 7, 2007

Meeting Type: B

Meeting Category: pre-IND

Meeting Location: FDA/White Oak
10903 New Hampshire Ave
Room 1415
Silver Spring, MD 20993

Application Number: PIND 74,284

Product Name: Zegerid omeprazole/sodium bicarbonate
immediate release powder for oral suspension(20mg
omeprazole)
Zegerid omeprazole/sodium bicarbonate immediate
release capsules

Received Briefing Package January 8, 2007

Sponsor Name: Schering-Plough Healthcare Products

Meeting Requestor: William Cochran
Manager, Regulatory Affairs

Meeting Chair: Andrea Leonard-Segal, M.D., Director

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Prior to the February 8, 2007 meeting, FDA verified that Santarus had shared the FDA's comments and recommendation with SPHC.

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20 mg Powder for Oral Suspension

1. Because the container-closure will not change, does FDA agree that the current expiry dating for Zegerid Powder can be applied to the OTC version?

FDA Preliminary Response:

Yes, it can be applied if the CMC package of the OTC version is identical to the prescription Zegerid as you stated in the briefing package. If there are differences in CMC between OTC and prescription Zegerid, the actual expiry period granted is a review issue.

20 mg Capsule

The following changes to the capsule are anticipated to accommodate the OTC indication (see Exhibit 8.2.1 for more details):

The capsule shell will be all white (Deletion of FD&C Blue #1 and FD&C Red #3 in the capsule shell) as opposed to the half blue/half white color of the Rx product. The capsule imprint graphic will change but the qualitative composition of the imprinting ink will not. A tamper evident band ((b) (4) Gelatin using same FD&C Blue #1 dye as is found in the Rx capsule shell) will be added to the capsule as per the requirements of 21 CFR 211.132. The tamper evident band is on the outside of the capsule shell and will not be in contact with the capsule contents.

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2. We intend to use the current Rx marketed product (blue/white capsule without tamper evident band) in the proposed comparative bioavailability study for the 20 mg capsule product? We plan to demonstrate that the banded capsule meets the current approved dissolution specification for the unbanded capsule. Does the Agency agree with this approach?

FDA Preliminary Response:

The approach appears acceptable provided that 1) virtually, no changes are made to omeprazole drug substance and/or no higher than level 1 changes to the manufacturing site/processes of the proposed omeprazole OTC IR 20 mg capsules other than for coloring agents and packaging of the final OTC IR 20 mg products and 2) dissolution testing meets the currently approved dissolution specification and shows similar dissolution profiles between the currently marketed Zegerid 20 mg IR capsules and the proposed OTC omeprazole IR 20 mg capsules.

3. Schering-Plough will commit to placing the first three commercial lots of 20 mg OTC capsules on stability post-approval (as will be outlined in the stability commitment submitted in the OTC NDA). Would the Agency agree that the changes bulleted above to the capsule would not require generation of pre-market stability data based on full cross-reference being granted to the Rx NDA and stability data contained therein. Would the Agency agree that the OTC NDAs (with changes as summarized above) could be granted approval of the Rx approved expiry dating based on the aforementioned proposal?

FDA Preliminary Response:

No, we disagree. Pre-market stability data will be required for the OTC NDAs on capsules because of the changes outlined on page 49 of the briefing package. The actual expiry period granted is a review issue.

3.1.2 Clinical/Safety Evaluation

4. Schering-Plough proposes to submit New Drug Applications under the provisions of section 505(b)(2) of the Food, Drug, and Cosmetic Act for the OTC marketing of Zegerid, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) in Capsule and Powder for Oral Suspension dosage forms. The prescription equivalents were approved by the Agency in NDAs 21-636 (Powder for Oral Suspension) and 21-849 (Capsule), sponsored by Santarus, Inc. of San Diego, CA. Using a comparative bioavailability study, discussed below, Schering-Plough proposes to compare Zegerid, immediate release omeprazole 20 mg and sodium bicarbonate, with Prilosec OTC 20mg (NDA 21-229). Accordingly, Schering-Plough intends to rely on the Agency's findings of safety, efficacy, and approvability for Prilosec OTC in order to support the NDA submission for Zegerid. Does the Agency agree that a 505(b)(2) application, supported by the data from the comparative bioavailability study outlined in Question 2 fulfills the requirements for approval?

FDA Preliminary Response:

A comparative bioavailability study would support a 505(b)(2) application, but additional data are needed (see below).

5. Schering-Plough's proposal for equivalence of each of the Zegerid dosage forms with Prilosec OTC will be based on a single dose pharmacokinetic study as per the attached protocol synopses (See Exhibits 8.1.1 and 8.1.2). The primary outcome measure will be bioequivalence to Prilosec OTC with respect to AUC. From a safety standpoint, FDA relied upon AUC when it approved Prilosec OTC tablets, since the drug's C_{max} was shown to be significantly higher than that for Prilosec Capsules, the prescription form of the drug. The relevant portion of the Summary Basis of Approval (SBA) for Prilosec OTC (NDA 21-299) is attached for reference (See Exhibit 8.1.3). Also, the single dose design is the basis by which the Office of Generic Drugs evaluates bioequivalence for the generic forms of omeprazole 20mg, as illustrated by a description of the ^{(b) (4)} Study No. 97273 in the SBA for ANDA 75-247 Is the Agency in agreement with this approach?

FDA Preliminary Response:

It should be noted that the word, "bioequivalence (BE)", is reserved only when the Agency's acceptance criteria for BE are met, i.e., the 90% confidence intervals of the ratio of least-square means for both $AUC_{(0-inf)}$ and C_{max} fall within 80-125%. Therefore, as stated in the proposed protocols, 90% confidence intervals should be calculated for the ratio of least-square means for both $AUC_{(0-inf)}$ and C_{max} of currently marketed Zegerid to omeprazole OTC 20 mg capsules.

In addition, it should be noted that post-marketing safety data, clinical trial safety and efficacy data and consumer study data were also submitted to support the Prilosec OTC switch. It would be erroneous to suggest that the safety of Prilosec OTC was based only on a pharmacokinetic comparison to the prescription omeprazole product.

Observed differences in the bioavailability of Zegerid and Prilosec OTC would need to be justified or supported by appropriate safety and/or efficacy data. If Zegerid is more bioavailable than Prilosec OTC, more safety information would be needed. If your product is less bioavailable, efficacy data would be needed.

Your product contains two active ingredients, omeprazole and sodium bicarbonate. Omeprazole magnesium is an approved nonprescription drug to treat heartburn and sodium bicarbonate a nonprescription ingredient generally recognized as safe and effective to relieve heartburn. Therefore, even if the omeprazole component of your product proves to be bioequivalent to Prilosec OTC this will be insufficient to support the prescription to OTC switch of Zegerid. You will need to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv). This may be achieved by conducting two clinical studies that demonstrate the contribution of each active ingredient to the efficacy of Zegerid to treat frequent heartburn.

6. Since Zegerid, like Prilosec OTC, will be taken on an empty stomach, the studies will be conducted in the fasting state only. Is the Agency in agreement with this approach?

*FDA Preliminary Response:
The approach appears acceptable.*

7. The Agency did not require or recommend additional safety studies as a condition for approval of the Zegerid 20 mg Rx NDAs'. As these NDAs were 505(b)(2) applications, Santarus referenced several NDAs for omeprazole, particularly those for Prilosec (NDA 19-810) for the safety portions. Does the Agency agree that no additional safety studies will be required for Zegerid, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) if, 1) its bioavailability profile is comparable to that of Prilosec OTC (omeprazole 20 mg), especially with respect to AUC, or 2) if Zegerid's profile is unexpectedly higher, that concerns about safety are adequately addressed by the safety database for omeprazole 40 mg, the highest strength of the prescription drug?

*FDA Preliminary Response:
If Zegerid is not bioequivalent to Prilosec OTC, but its PK profile is unexpectedly higher (for example, higher Cmax), then additional safety data would be needed. Omeprazole 40 mg is not approved for OTC use.*

3.1.3 Regulatory/Procedural

The sponsor of the NDAs for the prescription forms of Zegerid, Santarus granted Schering-Plough a full right of reference to its NDAs in order to facilitate our program for gaining OTC status for the drug.

8. Schering-Plough plans to submit the comparative bioavailability study information to the newly created file, IND 74,284, with appropriate references to the INDs and NDAs for the currently approved Zegerid products. Since the single dose of Zegerid 20mg to be given in the comparative bioavailability study falls well within the drug's margin of safety and is covered by its approved labeling. Please confirm that the standard 30-day IND hold will not apply.

*FDA Preliminary Response:
The standard 30-day IND hold would not apply if you can provide evidence that this product is the same as the approved prescription Zegerid product.*

3.1.4 Labeling

9. As with other OTC acid reducer drugs, we will likely distinguish Zegerid®, omeprazole/sodium bicarbonate Immediate Release (omeprazole 20 mg) from its prescription counterpart

(b) (4)

(b) (4)

FDA Preliminary Response:

(b) (4)

10. In view of Prilosec OTC's marketing history and the information in its NDA, does FDA agree that additional labeling comprehension and actual use studies are unnecessary?

FDA Preliminary Response:

Since your product contains two active ingredients, omeprazole and sodium bicarbonate, each of which is an approved nonprescription drug for heartburn, additional clinical studies that demonstrate the contribution of each ingredient to the efficacy of Zegerid to treat frequent heartburn are needed. Final labeling will depend on the results of these trials. If the labeling is substantially different from that of Prilosec OTC, then consumer comprehension (and/or behavior studies) may be needed. It is premature to discuss whether additional label comprehension and actual use trials are needed at this time.

3.1.5 Additional Comment:

Each 14 day course of your product should be packaged separately to further emphasize that 14 tablets constitute one course of therapy to treat frequent heartburn.

3.1.6 Additional Administrative Comments:

Comments shared today with you are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate the meeting discussion. As this meeting is a Pre-IND meeting, the comments from the Agency serve as guidance to you at

this preliminary stage. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the IND might identify additional comments or informational requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We encourage you to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

Your pre-IND has been assigned 74,284. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

When you submit your Investigational New Drug Application, please provide 6 copies.

3.2 Additional Discussion

SPHC opened the meeting with a review of the history of the development of the Zegerid products as prescription products and provided an argument to support why they should not have to conduct clinical trials for their proposed OTC products. The Division of Gastrointestinal Drug Products reviewed data for the prescription application that they felt fulfilled the combination policy for the indication being sought.

FDA responded that for the OTC indication, there are several other factors in the regulatory history that are important when determining what studies may be needed to support an OTC indication of frequent heartburn. They are as follows:

- Sodium bicarbonate is an active ingredient in the OTC drug monograph for the indication of relief of heartburn. From a regulatory perspective, it is no less of an active ingredient than an H2 blocker for this claim.
- In the past, FDA determined that the combination of an antacid and H2 blocker was acceptable for a claim of relief of heartburn. Companies would have to demonstrate

the contribution of each ingredient. For the combination of famotidine and an antacid, the sponsor was required to conduct clinical studies that demonstrated the contribution of each ingredient. (b) (4)

- FDA can not view sodium bicarbonate any differently than other active ingredients for heartburn relief, such as famotidine or ranitidine. So, if a company wanted to come in for a combination of an H2 blocker and omeprazole, FDA would expect them to fulfill the combination policy and conduct clinical trials that demonstrate the contribution of each ingredient.
- If FDA allowed a claim for frequent heartburn Zegerid without conducting clinical trials, (b) (4)

(b) (4) When Prilosec OTC was being developed, multiple studies were conducted to evaluate the effect for the relief of heartburn. None of these studies demonstrated a benefit. If however, omeprazole was combined with an antacid, it may be possible to show a treatment effect in part because of the antacid. FDA has to be consistent with how it deals with combinations such as that proposed for all of the OTC heartburn indications.

- (b) (4)

FDA reiterated to SPHC that the Zegerid formulation is a combination product and will have to follow the combination policy. The FDA stated that they understood that SPHC is using the sodium bicarbonate to protect the omeprazole from stomach acid degradation. If they combined an H2 blocker with omeprazole instead of the antacid, we would expect them to fulfill the combination policy and conduct two clinical studies. FDA explained that there is a regulatory history that needs to be considered and that SPHC's formulation can be compared to other products on the market like a famotidine and antacid combination, which was required to follow the combination policy by demonstrating the contribution of each ingredient. FDA determines what types of trials would be acceptable.

SPHC stated that they agree that the product is a combination drug, but that they felt that they were being held to a different standard with trying to switch the Zegerid product to the OTC marketplace. FDA explained that the reviewing divisions within the Office of New Drugs what information is needed to fulfill the combination policy which is based on different factors such as the indication, the class of drug and previous regulatory precedent. The review divisions have the discretion of deciding what information may be needed for the required studies to comply with the combination policy.

FDA stated that it understands that the sodium bicarbonate is included in Zegerid because of formulation issues, but explained that SPHC has the option of reformulating, as others have done, instead of combining another active ingredient to take care of the problem. FDA explained that the difficulty here is that SPHC is seeking a heartburn indication by combining two drugs that have heartburn indications on their own. In addition, FDA has permitted combinations of two different drugs to treat heartburn, one of them an antacid, and required that the clinical contribution of each ingredient be established through clinical studies.

SPHC noted that if they conducted a factorial study with their product, the individual components and placebo, that the arm with "naked" omeprazole would show no benefit because it would be destroyed by stomach acid. SPHC was told they would likely have to include an omeprazole formulation that demonstrated a clinical benefit superior than placebo. FDA stated that they generally do not accept a factorial study as valid if one of the single ingredient active arms includes a formulation of an active ingredient that is not effective. Also, this combination would also raise issues about whether it is rational to combine these ingredients for a frequent heartburn indication. In the past, FDA determined that the combination of an antacid and an H2 blocker was not rational for a prevention of meal induced heartburn claim. FDA stated that SPHC would need to provide support that this formulation is a rational combination for the indication sought. FDA stated that they had concerns regarding chronic use of omeprazole that SPHC would also have to address.

With regard to relying on the safety database for omeprazole 40 mg to support the safety of the Zegerid products (refer to Question 7), FDA explained that SPHC could provide the safety data from their current 40 mg prescription omeprazole product but that SPHC would need to compare and contrast the data with omeprazole 20 mg.

FDA encouraged SPHC to provide a written response to FDA outlining their argument as to why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv) with clinical studies. FDA stated that they would expedite a response to SPHC.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

SPHC/Santuras felt that an agreement to question 2 in regards to submitting the stability data was made at the first meeting in October 26, 2005 when Santuras met with the FDA and that the response that FDA provided for the February 8, 2007 meeting was different than the meeting minutes from the October 2005 meeting. Below is the response by the FDA given at the October 2005 meeting:

(October 2005) Question 5.

Does the Agency agree that Santarus can rely on the stability data generated for Zegerid 20-mg Rx capsules (packaged in bottles of 5 and 30) to support Zegerid OTC 20-mg

capsules (packaged in identical bottles of 14 and 28) and therefore, no additional stability studies are required?

FDA Response:

This proposal appears to be acceptable. See response to Question 6 below. It should be noted that NDA 21-849 is still under review.

(b) (4)



5.0 ACTION ITEMS

1. SPHC will provide the FDA with a written response about why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv).
2. FDA agreed to expedite the review SPHC's response.
3. FDA will follow-up on the stability issue and possible agreement made in October 2005.

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

Charles Ganley
3/9/2007 03:10:16 PM