

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022283Orig1s000**

**OTHER REVIEW(S)**

# Labeling Review for Zegerid OTC<sup>®</sup> Powder for Oral Suspension *Draft Labeling*

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<b>SUBMISSION DATES:</b>	December 14, 2012 and January 25, 2013
<b>NDA/SUBMISSION TYPE:</b>	022283 Resubmission/Class 2 Complete Response
<b>ACTIVE INGREDIENTS:</b>	Omeprazole 20 mg and Sodium Bicarbonate 1680 mg
<b>DOSAGE FORMS:</b>	Powder for Oral Suspension
<b>SPONSOR:</b>	MSD Consumer Care, Inc. Verna Mecadon, Executive Director, Regulatory Affairs 556 Morris Avenue Summit, NJ 07901-1330
<b>REVIEWER:</b>	Mary R. Vienna, M.H.A., DNRD/ODE IV
<b>TEAM LEADER:</b>	Ruth E. Scroggs, Pharm.D., DNRD/ODE IV
<b>Project Manager:</b>	Jeffrey A. Buchanan, DNCE/ODE IV

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## I. BACKGROUND

Zegerid OTC<sup>®</sup> powder for oral suspension [NDA 22-283] is a 505(b)(2) application, resubmitted December 14, 2012 in response to our December 28, 2011 Complete Response (CR) letter and as amended January 25, 2013. In its fourth review cycle, previous CR action dates are January 9, 2009 [first cycle], July 12, 2010 [second cycle] and December 28, 2011 [third cycle]. Subsequent to FDA's July 12, 2010 CR letter to the firm, the sponsor changed ownership from Schering-Plough Healthcare Products to MSD Consumer Care, Inc.

The January 25, 2013 amendment is submitted in response to our January 16, 2013 Information Request communicating a request for clarification of discrepancies between the annotated/draft labeling text and the submitted labels in the December 14, 2012 resubmission. The January 25, 2013 amendment aligns the annotated and draft labeling text with the December 14, 2012 labels.

A proton pump inhibitor, the proposed indication is for the treatment of frequent heartburn (occurring more than two times per week). The reference-listed product for the basis of the 505(b)(2) submission is Prilosec OTC<sup>®</sup>, NDA 021229. A related application for Zegerid OTC<sup>®</sup> capsules, NDA 022281, was approved December 1, 2009 for the same indication.

Labeling submitted December 14, 2012 appears in the following table:

Submitted Labeling	Representative of Following SKUs	Submission Date
1-count immediate container (1-dose packet)	Immediate container (1-dose packet) proposed for use with the 14-and 2-count package sizes.	December 14, 2012
2-count sample carton label	None	December 14, 2012
14-count carton label	None	December 14, 2012

We compare the proposed labeling submitted on December 14, 2012 to the labeling reviewed December 2, 2011, during the 3<sup>rd</sup> cycle review period and the last approved labeling for Zegerid OTC<sup>®</sup> capsules [NDA 022281 S-006 approved on September 18, 2012].

## II. REVIEWER'S COMMENTS

### A. Powder for Oral Suspension, 2- count sample and 14-count cartons

#### i. Outer Carton Label Outside Drug Facts

- a. The outer carton label for each count size is identical to the respective 2-count sample and 14-count outer carton labels reviewed December 2, 2011, except for the movement of "Sample Not for Sale" text on the 2-count sample carton from the center top section of the principal display panel to the right flap of the carton, centered above the copyright and manufacturer information.

**Comment: this is acceptable. Please remind the firm that the "New" flag located on the PDP's upper left margin should be removed after 6 months.**

#### ii. Outer Carton Drug Facts Label

##### a. *Warnings*

An additional bullet is added to the Warnings section "**Stop use and ask a doctor if**". The text of the bulleted statement reads "[bullet] you get diarrhea" as directed by the NDA 022281 FDA supplement request letter of February 16, 2012. This bullet is placed as the last (fourth) bullet, as requested in the NDA 022281 S-006 approval letter of September 18, 2012. To accommodate the addition of this new bullet, the bullet format in the preceding Warnings subsection "Ask a doctor or pharmacist before use if you are" is re-aligned from:

**Drug Facts (continued)**  
Ask a doctor or pharmacist before use if you are taking  
■ warfarin, clopidogrel or cilostazol (blood-thinning medicines)  
■ prescription antifungal or anti-yeast medicines ■ diazepam  
(anxiety medicine) ■ digoxin (heart medicine) ■ tacrolimus  
(immune system medicine)  
■ prescription antiretrovirals (medicines for HIV infection)  
■ any other prescription drugs. Sodium bicarbonate may interact  
with certain prescription drugs.

to:

**Drug Facts (continued)**  
Ask a doctor or pharmacist before use if you are taking  
■ warfarin, clopidogrel or cilostazol (blood-thinning medicines)  
■ prescription antifungal or anti-yeast medicines ■ diazepam  
(anxiety medicine) ■ digoxin (heart medicine) ■ tacrolimus  
(immune system medicine) ■ prescription antiretrovirals  
(medicines for HIV infection) ■ any other prescription drugs.  
Sodium bicarbonate may interact with certain prescription drugs.

**Comment: this is acceptable and consistent with class labeling required for all omeprazole drug products.**

b. **Other Sections/Issues**

The labeling meets format specifications in 21 CFR 201.66.

**Comment: this is acceptable.**

iii. **Immediate Container Label (1 dose packet) for 2-count sample and 14-count cartons**

General: One packet is proposed to serve as a unit-dose in the 2-count sample and the 14-count cartons.

a. The immediate container label is identical to the one reviewed and found acceptable in the December 2, 2011 labeling review.

**Comment: this is acceptable.**

### III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Zegerid OTC<sup>®</sup> powder for oral suspension labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 1-count immediate container (1-dose packet), 2-count sample carton, and 14-count carton labels submitted December 14, 2012.

Please remind the sponsor that the “New” statement must be removed from the label and labeling, wherever it appears, 6 months after introduction of the label into the OTC marketplace.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R VIENNA  
03/19/2013

RUTH E SCROGGS  
03/19/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 022283	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zegerid® OTC Established/Proper Name: Omeprazole and Sodium Bicarbonate Dosage Form: powder for oral suspension Strengths: 20mg/1680mg		
Applicant: MSD Consumer Care, Inc.		
Date of Receipt: 06-30-2011		
PDUFA Goal Date: 12-20-2011		Action Goal Date (if different):
Proposed Indication(s): Treats frequent heartburn		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 021229, Prilosec OTC™ 20mg tablets	Pharmacokinetic data

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Pharmacokinetic studies to bridge proposed Zegerid powder to Prilosec OTC (referenced drug)

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Prilosec OTC™ (omeprazole magnesium) 20mg delayed release tablets	021229	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application seeks the approval of omeprazole and sodium bicarbonate (Zegerid), rather than omeprazole magnesium (Prilosec OTC) for the OTC indication of frequent heartburn, and provides for a change in dosage form from tablet to powder.

This application is not an Rx to OTC switch for Zegerid, as frequent heartburn is a new indication for Zegerid and the application relies on the Prilosec NDA (021229) for efficacy.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): NDA 021636 Zegerid (omeprazole; sodium bicarbonate) 20mg/1.68Gm, powder for solution. This is the Rx version of the proposed OTC product.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 022281 Zegerid™ OTC (omeprazole; sodium bicarbonate ) 20mg/1160mg capsule; NDA 021849 Zegerid (omeprazole; sodium bicarbonate) 20 and 40mg/1.1Gm, capsule; approved generics for capsule are listed in Orange Book

### PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO   
*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO   
*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *June 10, 2008*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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MARY R VIENNA  
12/23/2011

**MEMORANDUM**

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

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DATE: December 14, 2011

TO: E. Dennis Bashaw, Pharm.D.  
Director,  
Division of Clinical Pharmacology III, OTS/OCP

FROM: Jyoti B. Patel, Ph.D.  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.  
Chief, Bioequivalence Branch,  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 22-283, *Zegrid OTC*  
(*omeprazole/sodium bicarbonate*) powder for oral  
suspension, sponsored by MSD Consumer Care, Inc.

At the request of the Division of Clinical Pharmacology III, OTS/OCP, the Division of Bioequivalence and GLP Compliance, conducted an audit of the clinical and bioanalytical portions of the following study:

**Study Number:** CL2010-12  
**Study Title:** "A Single Dose, Comparative, Open-label, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid® Powder for Oral Suspension 20 mg and Prilosec 40 mg Capsule in Healthy Subjects"

The inspection and data audit of the clinical portion of the above study were conducted at Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services, San Antonio, Texas from 10/24/2011 to 11/02/2011. The inspection and data audit of the analytical portion were conducted at [REDACTED] (b) (4)

[REDACTED]

Following the inspections, no Form FDA 483 was issued at the analytical site; however, Form FDA 483 was issued at the clinical site [Attachment 1]. As of this writing, no response

has been received from Worldwide Clinical Trials. Provided below are the Form FDA 483 observations and DBGC's evaluation.

**Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services, San Antonio, Texas:**

- 1) Failure to ensure that an investigation was conducted in accordance with the protocol. Specifically, the "Procedures" section of the protocol, located on page 46 of 108 [Attachment 2], states that "PK plasma samples will be placed in a storage freezer at - 20°C or lower within 60 minutes of blood draw." The following blood samples collected at 90 minute time point, during treatment period 2 on 1/29/2011 were placed in storage freezer after 60 minutes of collection:
  - a. Blood sample for subject #101 was frozen 63 minutes after collection.
  - b. Blood sample for subject #102 was frozen 61 minutes after collection.
  - c. Blood sample for subject #121 was frozen 68 minutes after collection.
  - d. Blood sample for subject #122 was frozen 66 minutes after collection.
  - e. Blood sample for subject #123 was frozen 64 minutes after collection.
  - f. Blood sample for subject #124 was frozen 62 minutes after collection.

Stability studies for omeprazole (performed at the analytical site, included in the NDA submission) show that omeprazole is stable in human plasma at room temperature for at least 26 hrs [Attachment 3]. The above samples were placed in a storage freezer slightly more than 60 minutes after collection. This observation should not impact the integrity of omeprazole in the plasma samples.

**Conclusions:**

Following the inspections of [REDACTED] (b) (4)

[REDACTED] DBGC recommends that the study data should be accepted for review.

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

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Jyoti B. Patel, Ph.D.

**Final Classifications:**

**VAI: Worldwide Clinical Trials Drug Development Solutions,  
Clinical Research Services, San Antonio, Texas**

**FEI: 3006724658**

**NAI:**

(b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGC/Salewski/Haidar/Skelly/Dejernet/Patel/CF (HFD-48)

OTS/OCP/DCP3/Bashaw/Lee

OND/ODE IV/DNCE/Vienna

HFR-SW1540/Martinez (BIMO)/Ramirez

HFR-SW1515/Bias (BIMO)

HFR-SW150/Turcovski (DIB)

Draft: JBP 12/14/2011

Edit: MFS 12/14/2011

OSI: 6249; O:\BE\EIRCOVER\22283msd.ome.doc

FACTS: 1317531

**Attachments:**

**Attachment 1: FORM FDA 483 issued at the clinical site; Protocol deviation involving criteria and procedures form**

**Attachment 2: Clinical protocol (page 46 of 108)**

**Attachment 3: Stability study results for omeprazole in human plasma**

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/s/  
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JYOTI B PATEL  
12/14/2011

MICHAEL F SKELLY  
12/15/2011  
Skelly signing on behalf of Dr. Haidar

# Labeling Review for Zegerid OTC Powder for Oral Solution *Draft Labeling*

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**SUBMISSION DATES:** June 29, October 13, 2011

**NDA/SUBMISSION TYPE:** 22-283 Complete Response

**ACTIVE INGREDIENTS:** Omeprazole 20 mg and Sodium bicarbonate 1680 mg

**DOSAGE FORMS:** Powder for Oral Suspension

**SPONSOR:** MSD Consumer Care, Inc.  
Paulette Midgette, Manager, Regulatory Affairs  
556 Morris Avenue  
Summit, NJ 07901-1330

**REVIEWER:** Ruth E. Scroggs, Pharm.D., DNRD, ODE IV

**TEAM LEADER:** Colleen Kane Rogers, Ph.D., DNRD, ODE IV

**Project Manager:** Mary R. Vienna, R.N., M.H.A., DNCE, ODE IV

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## I. BACKGROUND

Zegerid OTC Powder for Oral Solution [NDA 22-283] is a 505(b)(2) application, resubmitted June 30, 2011 in response to our July 12, 2010 Complete Response (CR) letter and as amended October 13, 2011. In its third review cycle, previous CR action dates are January 9, 2009 [first cycle] and July 12, 2010 [second cycle]. Subsequent to FDA's July 12, 2010 CR letter to the firm, the sponsor changed ownership from Schering-Plough Healthcare Products to MSD Consumer Care, Inc.

The October 13, 2011 amendment is submitted in response to our October 7, 2011 Information Request communicating a labeling comment to 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.

A proton pump inhibitor, the proposed indication is for the treatment of frequent heartburn (occurring more than two times per week). The reference-listed product (RLP) for the basis of the 505(b)(2) submission is Prilosec OTC, NDA 21-229. A related application for Zegerid OTC capsules, NDA 22-281, was approved December 1, 2009 for the same indication.

The prescription Zegerid 20 mg Powder for Oral Suspension is NDA 21-636. Unique to this product (capsules and powder) is the presence of sodium bicarbonate to help with absorption of the omeprazole active ingredient. Sodium bicarbonate protects the omeprazole long enough to allow absorption, therefore, it is not an antacid in this preparation.

Labeling submitted June 29, 2011 and October 13, 2011 appears in the following table.

Submitted Labeling	Representative of Following SKUs	Submission Date
SKU: Carton, 14-count	SKU: none	June 29, 2011
SKU: Carton, 2-count	SKU: none	October 13, 2011
SKU: Immediate container (1-dose packet), 2-count & 14-count	Immediate container (1-dose packet) proposed for use with the 14-and 2-count package sizes.	June 29, 2011

We compare the proposed labeling submitted on June 29, 2011 and October 13, 2011 to the labeling reviewed June 29, 2010, during the 2<sup>nd</sup> cycle review period and the last approved labeling for Zegerid OTC capsules, [S-005 on July 25] and for Prilosec OTC [S-023 on August 29, 2011].

## II. REVIEWER'S COMMENTS

### A. Powder for Oral Suspension, 2- count sample and 14-count retail

#### i. Outer Carton Label Outside Drug Facts

- a. The PDP for each count size is identical to the respective 2-count PDP and 14-count PDP reviewed June 29, 2010.  
**Comment: this is acceptable. Please remind the firm that the “New” flag located on the PDP’s upper left margin should be removed after 6 months.**
- b. The “Tips” located on the top panel for the 2 count and left flap for the 14-count is identical to the “Tips” reviewed June 29, 2010, except for the editorial deletion of the “periods” at the end of each tip as suggested in our July 12, 2010 CR letter.  
**Comment: this is acceptable.**
- c. The change in ownership and address are revised to reflect the transfer in ownership from Schering-Plough Health Care Products, Inc. to MSD Consumer Care, Inc.

from:

 (b) (4)

XXXXX-XX/XXXX-XX-XXX”

to:

“© Copyright & Distributed by MSD Consumer Care Inc., PO Box 377, Memphis TN 38151 USA, a subsidiary of Merck & Co. Inc. Whitehouse Station NJ USA. All rights reserved. Product of Spain. XXXXX-XX/XXXX-XX-XXX”

For the 2-count, this information is located on the right flap, beneath “Sample Not for Sale” statement. For the 14-count, this information is located on the bottom panel beneath the Drug Facts box.

**Comment: this is acceptable.**

## ii. Outer Carton Drug Facts Label

### a. *Warnings*

Under the drug-drug interactions subheading, “Ask a doctor or pharmacist before use if you are,” the first bullet is revised to add cilostazol to the list of interacting drugs:

[bullet] warfarin, clopidogrel or cilostazol (blood-thinning medicines)

**Comment: this is acceptable and consistent with class labeling required for all omeprazole drug products.**

### b. *Other Sections/Issues*

The labeling meets format specifications in 21 CFR 201.66.

**Comment: this is acceptable.**

## iii. Immediate Container Label (1 dose packet) for 2-count sample and 14-count cartons

General: One packet is proposed to serve as a unit-dose in the 2-count sample and the 14-count carton.

a. The front panel is identical to the one reviewed and found acceptable in the June 18, 2010 labeling review.

**Comment: this is acceptable.**

b. The back panel is revised to reflect the change in ownership [submitted to this NDA April 5, 2011] and address are revised to reflect the transfer in ownership from Schering-Plough Health Care Products, Inc. to MSD Consumer Care, Inc. This information is located under the right column of Drug Facts on the packet’s lower right margin. Please see II.A.i.c. The firm confirms that the lot and expiration information will be printed on long side, white seal area of the front or on the back (dependant on the printing machine line set) of the Packet (1-dose) immediate container labeling (similar to the current Rx sachet).

**Comment: this is acceptable.**

(b) (4)

### III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Zegerid OTC Powder for Oral Solution in Carton (2- and 14-count packets) and Packet (1-dose) immediate container labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 1-dose immediate container (packet) and 14-count carton labels submitted June 29, 2011 and the 2-count sample carton label submitted October 13, 2011.

Please remind the sponsor that the “New” statement must be removed from the label and labeling, wherever it appears, 6 months after introduction of the label into the OTC marketplace.

### IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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RUTH E SCROGGS  
12/02/2011

COLLEEN K ROGERS  
12/02/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: September 12, 2011

Reviewer(s): Chi-Ming (Alice), Tu PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Carlos M. Mena-Grillasca, RPh, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name/ Strength: Zegerid OTC (Omeprazole and Sodium Bicarbonate)  
Powder for Oral Suspension, 20 mg/1680 mg

Application Type/Number: NDA 022283

Applicant/sponsor: Schering Plough

OSE RCM #: 2011-2597

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## **1 INTRODUCTION**

This review evaluates the container label and carton labeling submitted on June 29, 2011 for Zegerid OTC (Omeprazole and Sodium Bicarbonate) Powder for Oral Suspension, 20 mg/1680 mg, for areas of vulnerability that can lead to medication errors in response to a request from the Division of Nonprescription Clinical Evaluation.

### **1.1 REGULATORY HISTORY**

Zegerid OTC (Omeprazole and Sodium Bicarbonate) Powder for Oral Suspension, 20 mg/1680 mg, received a Complete Response on January 16, 2009 and on July 12, 2010. On June 29, 2011, the Applicant responded to the July 12, 2010 Complete Response Letter with additional information including proposed labels and labeling. DMEPA previously reviewed proposed container label and carton labeling for Zegerid OTC in OSE RCM #2010-161, dated April 27, 2010.

Zegerid OTC (Omeprazole and Sodium Bicarbonate) Capsule, 20 mg/1100 mg, is currently marketed.

## **2 METHODS AND MATERIALS REVIEWED**

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 29, 2011
- Carton Labeling submitted June 29, 2011
- Physician sample carton labeling submitted June 29, 2011

Additionally, since Zegerid OTC is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Zegerid OTC. The AERS search conducted on August 31, 2011 used the following search terms: trade name “Zegerid OTC” and verbatim terms “Zegerid OT%” and “omeprazole so%.” The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and Preferred Term (PT) “Product Quality Issues”. Since an AERS search was conducted in OSE Review #2010-161, the search date was limited from April 5, 2010 to August 30, 2011.

Our AERS search did not retrieve any report.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### **3 RESULTS**

Our review of the proposed label and labeling identified the following areas of concern:

1. The modifier “OTC” on the principal display panel is small and less prominent than the rest of the tradename “Zegerid.”
2. Lack of expiration date and lot number on the immediate container label.
3. The placement of the Drug Facts on the bottom panel of carton labeling. Drug Facts information is vital for consumers to administer the product correctly. As currently presented, the bottom panel may be overlooked by consumers and healthcare providers because Drug Facts information is typically not located on the bottom panel (i.e. Zegerid OTC capsules). Additionally, information on the bottom panel may be distorted during storage due to friction between the store shelf and the carton.

### **4 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes that the proposed container label and carton labeling introduce vulnerability that can lead to medication errors. We provide recommendations to the Division in Section 4.1 and to the Applicant in Section 4.2 to mitigate the risk of such errors. We request these recommendations be communicated to the Applicant for revision prior to approval.

#### **4.1 COMMENTS TO THE DIVISION**

The modifier “OTC” on the principal display panels is smaller and less prominent than the rest of the tradename “Zegerid”. DMEPA recommends revising the presentation of the tradename “Zegerid OTC” to be presented in uniform font size, type style, and color type. Additionally, DMEPA recommends that the entire tradename appear on the same line of the principal display panel.

DMEPA is aware that the Zegerid OTC capsules are approved with the same presentation of the proprietary name. We would request this change be made for both products.

#### **4.2 COMMENTS TO THE APPLICANT**

##### **A. Container Label**

1. Ensure that the expiration date is printed on the container label per 21 CFR 201.17.
2. Ensure that the lot number is printed on the container label per 21 CFR 201.18.

##### **B. Carton Labeling (Retail carton and physician sample)**

1. Drug Facts information is vital for consumers to administer the product correctly. As currently presented, the bottom panel may be overlooked by consumers and healthcare providers because Drug Facts information is typically not located on the bottom panel (i.e. Zegerid OTC capsules). Additionally, information on the bottom panel may be distorted during

storage due to friction between the store shelf and the carton. Therefore, we request that you revise the placement of Drug Facts information so that it is located on the back and side panel. Alternatively, a peel back label may be used to present the Drug Facts information but ensure that the symbol to peel back the label, and instructions on how to peel back the label are prominently displayed.

If you have further questions or need clarifications, please contact Cherye Milburn, project manager, at 301-796-2084.

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/s/  
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CHI-MING TU  
09/12/2011

CARLOS M MENA-GRILLASCA  
09/12/2011

CAROL A HOLQUIST  
09/12/2011

MEMORANDUM

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

---

DATE: August 22, 2011

TO: Director, Investigations Branch  
Dallas District Office  
4040 N. Central Expressway  
Suite 300  
Dallas, TX 75204

FROM: Martin K. Yau, Ph.D.  
Acting Team Leader-Bioequivalence Branch  
Division of Bioequivalence and Good Laboratory  
Practice Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2011, **High Priority CDER PDUFA NDA, Pre-Approval  
Data Validation Inspection**, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 22-283

DRUG: Zegerid OTC® (Omeprazole 20 mg/Sodium  
Bicarbonate 1680 mg) Powder for Oral  
Suspension

SPONSOR: MSD Consumer Care, Inc.  
556 Morris Avenue  
Summit, NJ 07901-1330

SPONSOR'S CONTACT: Paulette Midgette  
Manager, Regulatory Affairs  
TEL: 1-267-305-8731  
FAX: 1-908-473-3814

EMAIL ADDRESS: Not available

This memo requests that you arrange for an inspection of the clinical and analytical sites where the following bioequivalence study was conducted. **At the request of the Review Division, the inspections should be completed prior to November 18, 2011.**

**Study Number:** CL2010-12

**Study Title:** "A Single Dose, Comparative, Open-label, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid® Powder

Page 2 - BIMO Assignment, NDA 22-283, Zegerid OTC® (Omeprazole 20 mg/Sodium Bicarbonate 1680 mg) Powder for Oral Suspension

for Oral Suspension 20 mg and Prilosec 40 mg Capsule in Healthy Subjects”

**Clinical Site:** Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services  
2455 N.E. Loop 410, Suite 150  
San Antonio, TX 78217

**Clinical Investigator:** Cynthia A. Zamora, M.D.  
TEL: 1-210-635-1500  
FAX: Not available  
EMAIL ADDRESS: Not available

Please check the batch numbers of the test and reference drug formulations used in study CL2010-12 with descriptions in the documents submitted to the Agency. Samples of the test and reference drug formulations should be collected at the clinical site and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all 50 study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. Please determine if the subjects met the protocol inclusion/exclusion criteria. Also, please verify that the subjects were compliant with the trial regimen.

(b) (4)



(b) (4)

**Methodology:** LC-MS/MS (omeprazole in sodium heparinized human plasma samples; omeprazole-d<sub>3</sub> as the internal standard)

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

Following identification of the investigator, background materials will be forwarded directly. **An OSI scientist with specialized knowledge will participate in the inspection at** (b) (4) **to provide scientific and technical expertise.**

Headquarters Contact Person: Abhijit Raha, Ph.D.  
(301) 796-3708

cc:

CDER OSI PM TRACK  
OSI/DBGC/Salewski/Haidar/Dejernet/Raha/CF (HFD-48)  
OTS/OCF/DCP3/E. Dennis Bashaw (Director, DCP3), Sue-Chih Lee  
HFD-560/Mary Vienna (DNCE)  
HFR-SW1540/Joel Martinez (BIMO)  
HFR-SW1515/Alanna Bias (BIMO)  
HFR-SW150/Susan Turcovski (DIB)  
Draft: AR 8/22/2011  
Edit: MKY 8/22/2011  
OSI: 6249; O:\BE\assigns\bio22283b.doc  
FACTS: 1317531

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/s/  
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ABHIJIT RAHA  
08/22/2011

MARTIN K YAU  
08/23/2011

# OSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** August 3, 2011

**TO:** Associate Director for Bioequivalence  
Office of Scientific Investigations, HFD-48

**THROUGH:** E. Dennis Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology III, OTS/OCP

Sue-Chih Lee, Ph.D.  
Clinical Pharmacology Team Leader, OTS/OCP/DCP3

**FROM:** Mary Vienna  
Regulatory Project Manager, Division of Nonprescription Clinical Evaluation, HFD-560

**SUBJECT:** **Request for Biopharmaceutical Inspections**  
NDA 22-283  
Zegerid OTC (omeprazole/sodium bicarbonate) powder, 20mg/1680mg  
MSD Consumer Care, Inc.

**Study/Site Identification:**

The following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

**Study CL2010-12:** A single-dose, comparative, open-label, randomized, crossover bioequivalence study of omeprazole administered as Zegerid powder for oral suspension 20mg and Prlosec 40mg capsule in healthy subjects.

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
CL2010-12	Cynthia A. Zamora, M.D. Principal Investigator Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services(WCTCRS) 2455 N.E. Loop 410, Suite 150, San Antonio, TX 78217 210-635-1500	(b) (4)

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by November 30, 2011. We intend to issue an action letter on this application by December 30, 2011.

Should you require any additional information, please contact Mary Vienna, Regulatory Project Manager, 301-796-4150.

Concurrence: (Optional)

Name Sue Chih Lee, Clinical Pharmacology Team Leader

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/s/  
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MARY RUSSELL R VIENNA  
08/03/2011

# Labeling Review for Zegerid OTC™ Powder for Oral Solution Draft Labeling

**SUBMISSION DATES:** Letter date Received date  
January 13, 2010 January 14, 2010  
June 11, 2010 June 14, 2010  
June 22, 2010 June 23, 2010

**NDA/SUBMISSION TYPE:** NDA 22-283 / Class 2 Resubmission

**ACTIVE INGREDIENTS:** Omeprazole 20 mg and Sodium bicarbonate 1680 mg

**DOSAGE FORMS:** Powder for Oral Suspension

**SPONSOR:** Schering-Plough Healthcare Products  
Williams Cochran, Senior Manager, Regulatory Affairs  
56 Livingston Ave.  
Roseland, NJ 07068

**REVIEWER:** Ruth E. Scroggs, Pharm.D., DNRD, ODE IV

**TEAM LEADER:** Colleen Kane Rogers, Ph.D., DNRD, ODE IV

**PROJECT MANAGER:** Mary R. Vienna, R.N., M.H.A., DNCE, ODE IV

## I. BACKGROUND

NDA 22-283 for Zegerid OTC™ Powder for Oral Solution is a 505(b)(2) application submitted January 13, 2010 as a complete response to our January 16, 2009 complete response (CR) letter communicating several issues including a list of nine labeling comments. A proton pump inhibitor, it is indicated for the treatment of frequent heartburn (occurring more than two times per week). The reference-listed product for the basis of the 505(b)(2) submission is Prilosec OTC, NDA 21-229. A related application for Zegerid OTC capsules, NDA 22-281, was approved December 1, 2009 for the same indication.

The firm submitted revised labeling on June 22, 2010, in response to our June 16, 2010 labeling comments generated from our June 18, 2010 labeling review. In this submission, labeling includes the 2- and 14-count cartons. We compare the revised 2- and 14-count cartons to the labeling submitted June 11, 2010 in this second review amendment of our May 26, 2010 review.

## II. REVIEWER'S COMMENTS

### A. Powder for Oral Suspension, 2- and 14-count

i. **Outer Carton (outside of Drug Facts Label)**

Under the “Tips for managing heartburn”, the periods remain although we had recommended removal of the periods at the end of each statement for consistency with labeling of other drugs in this class. The firm confirmed that this recommendation was not addressed due to an oversight. **Comment: this is acceptable. This is a minor editorial change.**

ii. **Outer Carton Drug Facts Label**

- a. Under the *Warnings*, drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” the firm revised the first bullet to read “(bullet) warfarin or clopidogrel (blood-thinning medicine)”. **Comment: this revision is acceptable and addresses review recommendation #2.**
- b. Under the *Other Information* section heading, the firm revised bullet #2 that read [REDACTED] (b) (4) to read “read the directions and warnings before use”. This statement was revised to [REDACTED] (b) (4). **Comment: this revision is acceptable and addresses review recommendation # 3.**
- c. Under the *Other Information* section heading, the firm revised bullet #3 that read [REDACTED] (b) (4) to read “keep the carton. It contains important information.” This was revised to [REDACTED] (b) (4). **Comment: this revision is acceptable and addresses review recommendation # 3.**
- d. The firm submitted annotated Drug Facts labeling to meet format specifications set forth 21 CFR 201.66. **Comment: this is acceptable.**

### III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Zegerid OTC powder for oral solution in Carton (2- and 14-count packets) and Packet (1-dose) labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: the 2- and 14-count carton labels submitted on June 22, 2010 and 1-dose immediate container (packet) label submitted June 11, 2010.

We recommend the following minor editorial revision listed below.

Under the “Tips for managing heartburn”, remove the periods at the end of each statement for consistency with labeling of other drugs in this class.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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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/

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RUTH E SCROGGS  
06/29/2010

COLLEEN K ROGERS  
06/29/2010

# Labeling Review for Zegerid OTC™ Powder for Oral Solution Draft Labeling

**SUBMISSION DATES:** Letter date Received date  
January 13, 2010 January 14, 2010  
June 11, 2010 June 14, 2010

**NDA/SUBMISSION TYPE:** NDA 22-283 / Class 2 Resubmission

**ACTIVE INGREDIENTS:** Omeprazole 20 mg and Sodium bicarbonate 1680 mg

**DOSAGE FORMS:** Powder for Oral Suspension

**SPONSOR:** Schering-Plough Healthcare Products  
Williams Cochran, Senior Manager, Regulatory Affairs  
56 Livingston Ave.  
Roseland, NJ 07068

**REVIEWER:** Ruth E. Scroggs, Pharm.D., DNRD, ODE IV

**TEAM LEADER:** Colleen Kane Rogers, Ph.D., DNRD, ODE IV

**PROJECT MANAGER:** Mary R. Vienna, R.N., M.H.A., DNCE, ODE IV

## I. BACKGROUND

NDA 22-283 for Zegerid OTC™ Powder for Oral Solution is a 505(b)(2) application submitted January 13, 2010 as a complete response to our January 16, 2009 complete response (CR) letter communicating several issues including a list of nine labeling comments. A proton pump inhibitor, it is indicated for the treatment of frequent heartburn (occurring more than two times per week). The reference-listed product for the basis of the 505(b)(2) submission is Prilosec OTC, NDA 21-229. A related application for Zegerid OTC capsules, NDA 22-281, approved December 1, 2009 has the same indication.

The firm submitted revised labeling on June 11, 2010, in response to our May 28, 2010 labeling comments. Submitted labeling includes the 2- and 14-count carton, and the immediate container (1-dose packet) see Table 1, (b) (4) and adding sections (b) (4) “How Zegerid OTC Works For Your Frequent Heartburn” and “Tips For Managing Heartburn” to the 2- and 14-count cartons. We address acceptability of this and other revisions in this first review amendment to our May 26, 2010 labeling review.

Table 1.

Submitted Labeling	Representative of Following SKUs
<b>SKU:</b> 14-count <ul style="list-style-type: none"> <li>• Carton</li> <li>• Immediate container (1-dose packet)</li> </ul>	<b>SKU:</b>  Immediate container (1-dose packet) proposed for use with the 14-and 2-count package sizes
<b>SKU:</b> 2-count <ul style="list-style-type: none"> <li>• Carton</li> </ul>	<b>SKU:</b> none

## II. REVIEWER'S COMMENTS

Our **bolded** reviewer comments state whether the labeling issue is acceptable or not acceptable and to which May 26, 2010 labeling review issue, our comments address, refer, or pertain, as applicable.

### A. Powder for Oral Suspension, 14-count

#### i. Outer Carton Label Outside Drug Facts

- a. To the bottom right PDP, the firm added the statement "EACH PACKET NET WT 0.19 OZ (5.6g)" under the "14 POWDER PACKETS" statement to meet the requirement under 21 CFR 201.62 that the net quantity must be expressed as weight in terms of avoirdupois pound and ounce. **Comment: this revision is acceptable and addresses recommendation #1.**
- b. The firm relocated the statement "One 14-Day Course of Treatment" from the lower right PDP to lower left PDP to accommodate revisions made in #1 above. **Comment: this revision is acceptable.**
- c. The firm proposes adding (b) (4) "How Zegerid OTC Works For Your Frequent Heartburn" and "Tips For Managing Heartburn" to the top side panel. **Comment: we agree with the sponsor's proposal to add (b) (4) to the top side panel, however, the formatting is not acceptable. 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. See section II.A.iv for discussion regarding (b) (4)**



- d. The firm removed [REDACTED] (b) (4)  
[REDACTED] **Comment: this revision is acceptable.**

ii. **Outer Carton Drug Facts Label**

a. **Active ingredient/Purpose**

The firm revised the purpose statement by changing the first letter of each major word in the sodium bicarbonate purpose statement to lower case except for the first word in the phrase. It now reads “Allows absorption of this omeprazole product”. **Comment: this revision is acceptable and addresses recommendation #3.**

b. **Warnings**

Under the drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” the firm revised the first bullet to read “(bullet) warfarin or Clopidogrel (blood-thinning medicines)”. **Comment: this statement is not acceptable. 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”). This recommendation revises recommendation #5 to be consistent with class labeling.**

c. **Directions**

The firm revised the Directions section so that the information under “14-Day Course of Treatment” is contained on the same panel, therefore moved to the bottom panel. Additionally, the arrow symbol directing consumers to the Drug Facts panel on the bottom of the carton is the only remaining character on its line (i.e., no longer shares its line with adjacent text), therefore is more prominent. **Comment: these are acceptable revisions and address recommendation #6.**

d. **Other Sections/Issues**

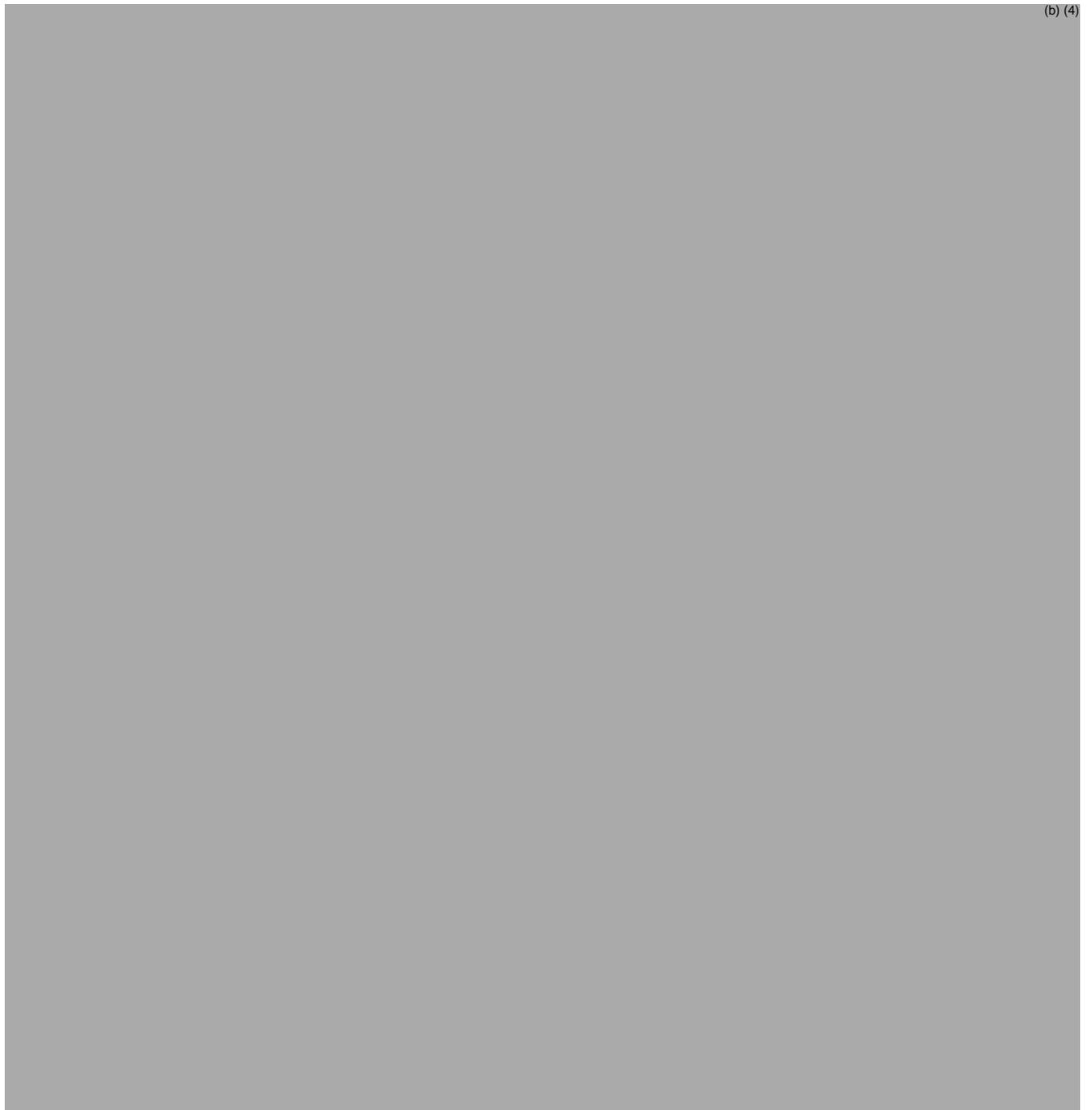
1. Other information

- [REDACTED] (b) (4)
- The fourth bullet storage conditions statement was revised from [REDACTED] (b) (4) to “store between 20° to 25°C (68° to 77°F)”.  
**Comment: this revision is acceptable.**
- The firm submitted annotated Drug Facts labeling to meet format specifications set forth 21 CFR 201.66. **Comment: this is acceptable.**

iii. **Immediate Container Label (1-dose packet) for 2-count Sample and 14-count Cartons**

- a. To the bottom right front panel, the firm added the statement “NET WT 0.19 OZ (5.6g)” under the statement “1 DAILY DOSE” to be consistent with the net quantity statement (expressed as a net weight) on the PDP. **Comment: this revision is acceptable and addresses recommendation #8.**
- b. On the back panel, under Other information, bullet 2, the firm revised the stated storage conditions statement from [REDACTED] (b) (4) to “store between 20° to 25°C (68° to 77°F)”. **Comment: this revision is acceptable.**
- c. On the Lower right corner back panel, the firm [REDACTED] (b) (4)  
**Comment: this revision is acceptable.**

[REDACTED] (b) (4)



**B. Powder for Oral Suspension, 2-count sample**

**i. Outer Carton Label Outside Drug Facts**

- a. To the bottom right PDP, the firm added the statement, “EACH PACKET NET WT 0.19 OZ (5.6g)” under the statement “2 POWDER PACKETS” to meet the requirement under 21 CFR 201.62 that the net quantity must be expressed as weight in terms of avoirdupois pound and ounce. **Comment: this revision is acceptable and addresses recommendation #1.**

- b. The firm replaced [REDACTED] (b) (4) with “Follow Samples with a 14-Day Course of Treatment” and moved it to the lower left.

**Comment: these revisions are acceptable and address recommendation # 2.**

- c. [REDACTED] (b) (4)

- d. The firm removed [REDACTED] (b) (4)  
**Comment: this revision is acceptable.**

- e. The firm replaced copy on the top panel with “How Zegerid OTC Works For Your Frequent Heartburn” and Tips for Managing Heartburn” copy, [REDACTED] (b) (4)  
**Comment: we agree with the sponsor’s proposal to add copy from the two sections to the top panel, however, the formatting is not acceptable. See section II.A.i.c.**

ii. **Outer Carton Label, Drug Facts**

a. **Purpose Statement**

The firm revised the purpose statement by changing the first letter of each major word in the sodium bicarbonate purpose statement to lower case except for the first word in the phrase. It now reads “Allows absorption of this omeprazole product”. **Comment: this revision is acceptable and addresses recommendation #3.**

b. **Warnings**

1. The firm deleted the period at the end of the Allergy Alert statement.  
**Comment: this revision is acceptable and addresses recommendation #4.**
2. Under the drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” the firm revised the first bullet to read “(bullet) warfarin or Clopidogrel (blood-thinning medicines)”. **Comment: this revision is not acceptable. See section II.A.ii.b.**

c. **Other Sections/Issues**

1. Other information

- [REDACTED] (b) (4)

- The fourth bullet storage conditions statement was revised from (b) (4) to “store between 20° to 25°C (68° to 77°F)”.  
**Comment: this revision is acceptable.**

## 2. Drug Facts Format

- The firm revised the carton’s left flap to contain the Drug Facts (continued) statement. **Comment: This revision is acceptable and addresses recommendation # 7.**
- The firm submitted annotated Drug Facts labeling. **Comment: the label meets format specifications set forth 21 CFR 201.66, therefore is acceptable.**

### III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

2-ct and 14-ct cartons:

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 (b) (4)

### IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

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RUTH E SCROGGS  
06/18/2010

COLLEEN K ROGERS  
06/18/2010

# Labeling Review for Zegerid OTC™ Powder for Oral Solution *Draft Labeling*

**SUBMISSION DATES:** January 13, 2010 / Received January 14, 2010

**NDA/SUBMISSION TYPE:** NDA 22-283 / Class 2 Resubmission

**ACTIVE INGREDIENTS:** Omeprazole 20 mg and Sodium bicarbonate 1680 mg

**DOSAGE FORMS:** Powder for Oral Suspension

**SPONSOR:** Schering-Plough Healthcare Products  
Williams Cochran, Senior Manager, Regulatory Affairs  
56 Livingston Ave.  
Roseland, NJ 07068

**REVIEWER:** Ruth E. Scroggs, Pharm.D., DNRD, ODE IV

**TEAM LEADER:** Colleen Kane Rogers, Ph.D., DNRD, ODE IV

**PROJECT MANAGER:** Mary R. Vienna, R.N., M.H.A., DNCE, ODE IV

## I. BACKGROUND

NDA 22-283 for Zegerid OTC™ Powder for Oral Solution is a 505(b)(2) application submitted January 13, 2010 as a complete response to our January 16, 2009 complete response (CR) letter communicating several issues including a list of nine labeling comments. A proton pump inhibitor, it is indicated for the treatment of frequent heartburn (occurring more than two times per week). A related application for Zegerid OTC capsules, NDA 22-281, was approved December 1, 2009 for the same indication. The reference-listed product for the basis of the 505(b)(2) submission is Prilosec OTC, NDA 21-229. The prescription Zegerid 20 mg Powder for Oral Suspension is NDA 21-636. Both the OTC powder and OTC capsules are approved for the heartburn indication. Other indications are prescription only.

Unique to this product (capsules and powder) is the presence of sodium bicarbonate to help with absorption of the omeprazole active ingredient. Sodium bicarbonate protects the omeprazole long enough to allow absorption, therefore, it is not an antacid in this preparation.

This submission provides for a proposed 14- and 2-count carton to hold 14 and 2 individual packets, respectively. A single package insert was submitted to cover both count sizes. Labeling submitted this cycle includes the following:

Submitted Labeling	Representative of Following SKUs
SKU: 14-count <ul style="list-style-type: none"> <li>• Carton</li> <li>• Immediate container (1-dose packet)</li> </ul>	[SKU]  Immediate container (1-dose packet) proposed for use with the 14-and 2-count package sizes.
SKU: 2-count <ul style="list-style-type: none"> <li>• Carton</li> </ul>	none

(b) (4)

This review addresses labeling submitted January 13, 2010. The proposed labeling is compared to labeling submitted first cycle and the subject of the IDS review of December 4, 2008. Other related labeling used for reference are the recently approved Zegerid OTC capsules 2-count sample (NDA 22-281 approved April 15, 2010), Zegerid OTC capsules (NDA 22-281 approved December 1, 2009) and Prilosec OTC labeling (NDA 21-229/S-013 approved September 9, 2009).

## II. REVIEWER'S COMMENTS

Reviewer comments (bolded, italic) state whether the labeling issue is acceptable or unacceptable and which CR letter labeling comment (*FDA labeling comment*) it addresses as applicable.

### A. Powder for Oral Suspension, 14-count

#### i. Outer Carton Label Outside Drug Facts

##### a. Principal Display Panel (front)

1. The upper left corner bears a "New" flag.  
**Comment: This is acceptable, however should be removed after six months of marketing.**
2. In the top, located above the proprietary name, the approved indication statement, "Treats Frequent Heartburn replaces the statement (b) (4) because other indications will still be prescription only.  
**Comment: These revisions are acceptable and address FDA labeling comment #3.**
3. The proprietary name Zegerid OTC™ displays the "OTC™" below the "rid" in Zegerid to be consistent with other products in the category.



(b) (4)

*Comment: Displaying the trade name on two separate lines is acceptable at this time and addresses FDA labeling comment #2. However, if we reconsider our position regarding the presentation/orientation of the proprietary names in this therapeutic category, then this approach may not be acceptable at some time in the future.*

- 4. The statement of identity is located in the lower left corner, below the proprietary name, with the sodium bicarbonate purpose statement revised from (b) (4) to “Allows Absorption of this Omeprazole Product”. This will allow the average consumer to understand the unique function of sodium bicarbonate in Zegerid OTC.

*Comment: This revision is acceptable and addresses FDA labeling comment #1.*

- 5. In the lower right corner of the PDP, an image of a Zegerid packet appears overlaid on a (b) (4) from the packet’s open end. The first cycle’s image of (b) (4) is removed.



(b) (4)

*Comment: This is acceptable.*

(b) (4)

- 6. Also in the lower right corner, the term “14 POWDER PACKETS” appears in the location where net quantity of contents would be located.

**Comment:** *This is unacceptable as a net quantity statement (see 21 CFR 201.62). The net quantity statement must be expressed as weight in terms of avoirdupois pound and ounce and may be expressed as a combination of numerical count and weight. The net quantity statement should be added below “14 POWDER PACKETS” on the PDP. For example “14 POWDER PACKETS EACH PACKET NET WT x.x OZ”.*

**b. Flaps**

1. On the top panel right flap, the space for the lot number and expiration location is indicated, adjacent to a barcode.

**Comment:** *This is acceptable and addresses FDA labeling comment #9.*

2. On the middle panel and back panel right side flaps, bar code symbols appear. The remaining flaps carry no text or code.

**Comment:** *These are all acceptable.*

**c. Top Panel (appears reduced in size below)**

The indication statement, proprietary name, image, and number of powder packets statement are identical to the PDP.

**Comment:** *This is acceptable.*



**ii. Outer Carton Drug Facts Label**

**a. Active ingredient/Purpose**

The purpose statement (b) (4) is revised to “Allows Absorption of this Omeprazole Product”.

**Comment:** *Although the statement is acceptable, the formatting is unacceptable and should be revised so that only the first word in the statement is upper case to read as: “Allows absorption of this omeprazole product” to be consistent with the approved Zegerid OTC capsules. This response addresses FDA labeling comment #1.*

b. *Warnings*

1. Under the drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” the first bullet reads: (bullet) warfarin (blood-thinning medicine).

***Comment: This statement is unacceptable as is because it needs to be updated to include clopidogrel as part of a class labeling change. The first bullet should be revised to read:***

“(bullet) warfarin or clopidogrel (blood-thinning medicines)”

***As a class, all proton pump inhibitors may decrease the efficacy of clopidogrel when used concomitantly. We combined the two warnings because consumers are more likely to consider clopidogrel and warfarin as blood thinning medicines. It is important to inform consumers to ask a doctor or pharmacist before use if taking clopidogrel and omeprazole together. The warning is based on data showing that omeprazole reduces the anti-blood clotting effect of clopidogrel bisulfate when the two drugs are taken together as was discussed in recent FDA advisories.***

2. Under the drug-drug interactions subheading “Ask a doctor or pharmacist before use if you are,” The sixth bullet is updated to read: “(bullet) prescription antiretrovirals (medicines for HIV infection)” because (b) (4) antiretroviral medications as a class are known to interact with omeprazole.

***Comment: This is acceptable. This proton pump inhibitor (PPI) class labeling revision is consistent with the revision made to the Prilosec OTC label in S-013 and prescription PPIs. Other antiretroviral medications, (b) (4) are known to interact with omeprazole.***

c. *Directions*

General. The Directions section is split between the back panel and the bottom of the carton.

**Comment: We are concerned about such a format. Important information for the consumer’s effective use of this product is placed on the bottom of the carton. This may be confusing to the consumer. We recommend that you do two things: 1) Start the “14-day Course of Treatment” section at the top of the panel on the bottom of the carton so that important directions are not split between sides of the carton and 2. increase the size of the arrow at the bottom of the box to alert consumers to additional important directions on the bottom of the box.**

1. **Bullet 3.** The word “although” remains and is not consistent with the approved Prilosec OTC label.

***Comment: This is acceptable.***

2. **Bullet 1.** Under the subheading “**14-Day Course of Treatment,**” the first bullet is revised to read: (bullet) “product should be taken at least 1 hour before eating in the morning” consistent with the approved label directions for prescription Zegerid Powder and Zegerid OTC Capsules. The firm agrees that there is a food effect on the product’s omeprazole absorption, therefore, the consumer’s administration should be well-separated from meal consumption. The firm further justifies that a time interval of one hour is fully satisfactory for this purpose, but a longer time is equally suitable.

*Comment: We agree with the firm’s rationale. This revision is acceptable and addresses FDA labeling comment #5.*

**d. Other Sections/Issues**

1. Use. The second bulleted statement is revised by inserting a period after “heartburn: and capitalizing the “t” in the “this drug may take 1 to 4 days for full effect” It now reads as appears below.



*Comment: This revision is acceptable and addresses FDA labeling comment #4.*

2. Other information. Bullet 4. The stated storage conditions are consistent with the Quality review dated December 3, 2008.

*Comment: This is acceptable.*

3. “Questions or Comments?” This section is revised as shown below adding the times when staff are available to answer phone calls next to the toll-free number.



*Comment: This is acceptable and addresses FDA labeling comment #6.*

4. Drug Facts format.

*Comment: The label meets format specifications set forth 21 CFR 201.66. This is acceptable.*

**iii. Immediate Container Label (1 dose packet) for 2-count sample and 14-count cartons**

General: One packet is proposed to serve as a unit-dose in the 2-count sample and the 14-count carton.

*Comment: This is acceptable.*

**a. PDP, outside of Drug Facts**



1. Upper left corner. The new flag is removed.  
*Comment: This is acceptable.*
2. A tamper evident statement is added at the top.  
*Comment: This is acceptable.*
3. The indication statement “Treats Frequent Heartburn” replaces the original prescription strength statement.  
*Comment: This is acceptable. See A.i.a.2 for more detail.*
4. The NDC number is deleted from the upper right corner, but appears on the carton.  
*Comment: This is acceptable.*
5. Upper right corner. The opening instructions are revised by adding the text “FOLD AT LINE TEAR AT (b)(4)” to the upper right corner. Similarly worded, but not identical text and scissors image are deleted from the right side and upper right corner respectively.  
*Comment: This is acceptable.*
6. Proprietary name “Zegerid OTC”  
*Comment: This is acceptable. See A.i.a.3 for more detail.*

7. Statement of identity/Purpose moved to lower left corner and purpose statement is revised.

*Comment: This is acceptable. See A.i.a.4 for more detail.*

8. "SEE BACK FOR DIRECTIONS FOR USE" is moved from the left side of the "Z" in the proprietary name to the lower left corner.

*Comment: This is acceptable.*

9. Lower right corner. "1 DAILY DOSE" is stated and may be intended as a net quantity statement.

*Comment: We recommend that the net quantity statement also be expressed as weight in terms of avoirdupois pound and ounce to be consistent with the net quantity statement on the PDP.*

- b. Back: The image of the packet back appears below.



1. The top line is revised to read: "READ OUTER CARTON [REDACTED] FOR WARNINGS AND COMPLETE PRODUCT INFORMATION." This directs the consumer to read the outer carton and package insert for Warnings and complete product information.

*Comment: This is acceptable.*

2. **Directions.** The first bullet under "14-day Course of Treatment" has been modified. See A.ii.c.2 for more detail.

*Comment: This is acceptable.*

3. **Directions.** The pediatric statement (children under 18 years of age...) has been modified to be consistent with current class labeling for omeprazole.

**Comment:** *This is acceptable.*

4. The words [REDACTED] (b) (4) are deleted [REDACTED] (b) (4)

**Comment:** *This is acceptable and addresses FDA labeling comment #8.*



(b) (4)

**B. Powder for Oral Suspension, 2-count sample****i. Outer Carton Label Outside Drug Facts****a. PDP:**

1. The lower right corner states

(b) (4)

*Comment: This statement is unacceptable and should be replaced by the statement "Follow Samples with a 14-Day Course of Treatment". This is consistent with the approved Zegerid Capsules and Prilosec OTC samples.*

2. The net quantity is missing.

*Comment: This is unacceptable and should be added. See A.i.a.6.*

**b. Top Panel:**

A sample statement is added to the upper left corner.

**Comment: This is acceptable.**

**ii. Outer Carton Drug Facts Label**

Drug Facts is added to the sample carton.

*Comment: This is acceptable and addresses FDA labeling comment # 7 stating that a Drug Facts panel on the 2-ct sample carton label as required by Section 502(c) of the Food, Drug and Cosmetic Act.*

**a. Warnings**

1. The allergy alert ends with a period.

*Comment: This is unacceptable. Under the subheading "Allergy Alert," delete the period from the statement to read: "Do not use if you are allergic to omeprazole".*

2. The warfarin drug-drug interaction warning is not updated to be consistent with omeprazole class labeling for clopidogrel.

*Comment: This is unacceptable. See II.A.ii.b.1*

3. The antiretroviral drug-drug interaction warning is updated to be consistent with omeprazole class labeling.

*Comment: This is acceptable.*

**b. Other Sections/Issues**

The carton's left flap contains a Drug Facts panel, however it is missing the Drug Facts (continued) statement.

*Comment: This is not acceptable and needs to be revised to add the statement "Drug Facts (continued)" (see 21 CFR 201.66(c)(1)).*

**iii. Immediate Container Label (1 dose packet) for 2-count sample**

See review at A.iii.

**iv. Package Insert (PI)**

See review at A.iv.

### III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

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  <sup>(b) (4)</sup> 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)

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

**IV. SUBMITTED LABELING**

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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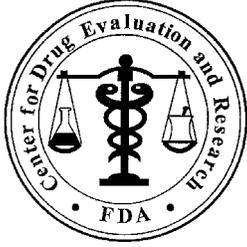
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/s/

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RUTH E SCROGGS  
05/26/2010

COLLEEN K ROGERS  
05/26/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 27, 2010

To: Andrea Leonard-Segal, M.D., M.S.  
Director, Division of Nonprescription Clinical Evaluation  
Office of Nonprescription Products

Through: Kellie Taylor, Pharm.D., M.P.H., Associate Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, Pharm.D., Acting Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Zegerid OTC (Omeprazole and Sodium Bicarbonate)  
Powder for Oral Suspension 20 mg/1680 mg

Application Type/Number: NDA 022283

Applicant: Schering-Plough

OSE RCM #: 2010-161

## **EXECUTIVE SUMMARY**

We evaluated the proposed container labels, carton labeling, Drug Facts labeling, (b) (4) from a medication error perspective and noted areas with needed improvement. The presentation of the information in the Drug Facts on the proposed carton labeling can be improved to help minimize the risk of administering the drug incorrectly. As presented now, the drug facts are located on the back panel and the bottom panel. Product information is typically not located on the bottom and thus, may be overlooked by the patient.

## **1 INTRODUCTION**

This review was written in response to a request from the Division of Clinical Nonprescription Evaluation to evaluate the revised container label, carton and drug facts labeling for Zegerid OTC (Omeprazole and Sodium Bicarbonate) powder for suspension.

### **1.1 REGULATORY HISTORY**

On March 10<sup>th</sup>, 2008 the Applicant submitted a 505(b)(2) application for Zegerid OTC that provides for capsules of omeprazole 20 mg and sodium bicarbonate 1100 mg. Nine days later on March 19<sup>th</sup>, 2008 the Applicant submitted a second 505(b)(2) application for Zegerid OTC that provides for powder for oral suspension of omeprazole 20 mg and sodium bicarbonate 1680 mg. The reference listed drug is Prilosec OTC (NDA 021229). Zegerid OTC capsules we approved on December 1, 2000, under NDA 022281. However Zegerid OTC powder for oral suspension was not approved during the first review cycle and received a complete response on January 16, 2009. The Applicant responded to the complete submission on January 14, 2010.

### **1.2 PRODUCT INFORMATION**

Zegerid OTC (Omeprazole and Sodium Bicarbonate) powder for oral suspension is a product line extension of Zegerid OTC capsules. Zegerid OTC powder for oral suspension is identical to Zegerid OTC capsules in regards to all product characteristics except dosage form (powder for oral suspension vs. capsules) and amount of sodium bicarbonate contained in each dose (1680 mg vs. 1100 mg). Although the two products contain a different amount of sodium bicarbonate, the sodium bicarbonate does not provide a therapeutic action for the indication of treatment of frequent heartburn. Sodium Bicarbonate is an active ingredient that allows for absorption of the omeprazole which is the active ingredient responsible for the therapeutic action. Since the sodium bicarbonate does not provide a therapeutic action, the capsules and powder for suspension are therapeutically equivalent.

## **2 METHODS AND MATERIALS**

### **2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE**

Since, Zegerid OTC is currently marketed, DMEPA conducted a search of the Adverse Event Reporting System (AERS) on April 5, 2010, using active ingredients “Sodium Bi%” and “Omeprazo%”, trade name “Zeg%” and verbatim substance names “Zeg%”, “omep%”, and “Sodium Bi%” along with the MedDRA reaction terms “Medication Errors” (HLGT), “Product Quality Issue” (PT) and “Product Label Issue” (HLT). Additionally, since an AERS search was conducted in OSE Review #2008-610 (Zegerid OTC Proprietary name review), on April 28, 2008, DMEPA limited our search from April 28, 2008, to the present.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

The search strategy described above did not identify any cases of medication errors reports involving Zegerid OTC. However, since medication errors are known to be under reported a lack of reports can not guarantee that errors are not occurring, only that the errors are not being reported to the FDA.

## **2.2 LABELS AND LABELING**

The Applicant submitted container labels (see Appendix A), carton labeling (see Appendix B), and package insert labeling (see Appendix C) on January 14, 2010. DMEPA used Failure Mode and Effects Analysis (FMEA)<sup>1</sup> in our evaluation of the labels, labeling, and packaging configuration. DMEPA reviewed the approved labeling for Zegerid OTC capsules to ensure the labels and labeling are consistent for both products (see Appendix D).

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Our evaluation of the labels and labeling noted that the placement of the Drug Facts on the carton labeling should be revised to help minimize the risk of patients overlooking important information that will appear on the bottom panel. We also noted that the proprietary name modifier “OTC” lacks prominence in comparison to Zegerid. We provide our recommendations for the presentation of the proprietary name in Section 3.1 *Comments to the Division* and for the carton labeling in Section 3.2, *Comments to the Applicant*. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Catherin Carr, OSE Regulatory Project manager, at 301-796-2311.

### **3.1 COMMENTS TO THE DIVISION**

The modifier “OTC” on the primary display panels is smaller and less prominent than the rest of the tradename “Zegerid”. DMEPA recommends revising the presentation of the tradename “Zegerid OTC” to be presented in uniform font size, type style, and color type. Additionally, DMEPA recommends that the entire tradename appear on the same plane on the primary display panel.

DMEPA is aware that the Zegerid OTC capsules are approved with the same presentation of the proprietary name. We would request this change be made for both products. However, since it’s currently on the market we will defer to the Division on whether or not the prominence of the proprietary name be revised for this product.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3.2 COMMENTS TO THE APPLICANT

The presentation of the Drug Facts panel on the proposed carton labeling can be improved to help minimize the risk of administering the drug incorrectly. As presented now, the Drug Facts panel is located on the back panel and the bottom panel of the carton labeling. Product information is typically not located on the bottom panel and thus, may be overlooked by the patients and healthcare providers or may be distorted during storage because of friction caused between the shelf or storage unit and the bottom panel of the carton. Additionally, we note your carton labeling for the Zegerid OTC Capsules does not contain Drug Facts on the bottom Panel.

Since the information on the bottom panel is vital for consumers to administer the product correctly and there is other important information such as the contact number located in this section of Drug Facts, we recommend revising the presentation of the Drug Facts panel to ensure they do not appear on the bottom panel. If space allows, relocate the bar code, lot number and expiration date to the bottom panel and place the Drug Facts information on the back and side panels. However, if the space is insufficient to accomplish this we suggest the following alternatives:

1. Revise the physical carton to have an additional cardboard flap that would attach to the bottom panel and fold up to the back panel where the Drug Facts are located. This would allow for the flap to be folded downward and remain attached to the bottom panel effectively elongating the back panel so that the Drug Facts could be shown on a continuous panel. This cardboard panel is different from a “peel back” label seen on OTC products. Traditional peel back labels have several pieces of thin paper attached to each other and fold out to reveal information. However these peel back labels contain vital information and can be easily torn off and removed from the carton or container. Additionally, patients and healthcare practitioners may be unaware of the need to peel back the label to reveal the complete Drug Facts label<sup>2</sup>
2. If the addition of a cardboard flap is not feasible, utilize traditional peel back labels to include Drug Facts. However, ensure that the symbol to peel back the labels and the instructions on how to peel back the labels are prominently displayed.

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<sup>2</sup> Institute for Safe Medication Practices. Medication Safety Alert. Unrecognized peel-back labels on OTC drugs; January 14, 2010.

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NDA-22283	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	Zegerid OTC (omeprazole 20 mg & sodium bicarbonate 1680mg) powder.

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/s/

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ZACHARY A OLESZCZUK  
04/27/2010

KELLIE A TAYLOR  
04/27/2010

CAROL A HOLQUIST  
04/28/2010

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 22-283	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Zegerid® OTC Established/Proper Name: Omeprazole and Sodium Bicarbonate Dosage Form: powder for oral suspension Strengths: 20 mg/1680 mg		
Applicant: Schering-Plough Healthcare Products, Inc.		
Date of Receipt: 03-20-2008		
PDUFA Goal Date: 01-20-2009	Action Goal Date (if different):	
Proposed Indication(s): Treats frequent heartburn		

**GENERAL INFORMATION**

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If “YES,” proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES  NO

*If “YES “contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 21-229, Prilosec OTC™ 20 mg tablets	Pharmacokinetic data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Pharmacokinetic studies to bridge proposed Zegerid powder to Prilosec OTC (referenced drug)

**RELIANCE ON PUBLISHED LITERATURE**

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #6.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO”, proceed to question #6*

*If “YES”, list the listed drug(s) identified by name and answer question #5(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.*

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Prilosec OTC™ (omeprazole magnesium) 20 mg delayed release tablets	21-229	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES  NO

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b. Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The change from the listed drug: the application seeks the approval of omeprazole and sodium bicarbonate, rather than omeprazole magnesium; and provides for a change in dosage form from tablet to powder.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If **“YES”** and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If **“NO”** or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): NDA 21-636 Zegerid (Omeprazole; sodium bicarbonate) 20 mg powder for suspension.

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If **“NO”**, proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 21-849 Zegerid (Omeprazole; sodium bicarbonate) 20 mg and 40 mg capsule; NDA 21-636 Zegerid (Omeprazole; sodium bicarbonate) 40mg powder for suspension.

**PATENT CERTIFICATION/STATEMENTS**

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 4786505, 4853230, 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s): 4786505, 4853230, 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received: June 10, 2008

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

*If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?*

YES  NO

*Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.*

YES  NO

Date Received:

*Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.*

YES  NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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/s/

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Mary R Vienna  
1/6/2009 09:55:36 AM  
CSO



**Addendum  
To OTC Drug Labeling Review for  
Zegerid OTC Powder for Oral Suspension**

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**Division of Nonprescription Regulation Development • Office of Nonprescription Products**  
Center for Drug Evaluation and Research • Food and Drug Administration

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<b>SUBMISSION DATE:</b>	April 24, 2008	<b>RECEIVED DATE:</b>	April 28, 2008
<b>REVIEW DATE:</b>	December 4, 2008		
<b>NDA/SUBMISSION TYPE:</b>	NDA 22-283/N-000 (BL)		
<b>SPONSOR:</b>	Schering-Plough HealthCare Products, Inc. William Cochrane Sr. Manager, Regulatory Affairs (908)473-1858		
<b>DRUG PRODUCT(S):</b>	Zegerid OTC Powder for Oral Suspension		
<b>ACTIVE INGREDIENT (PHARMACOLOGICAL CATEGORY):</b>	omeprazole (acid reducer) sodium bicarbonate (assists in the absorption of omeprazole)		
<b>LABELING SUBMITTED:</b>	14-ct carton label [REDACTED] (b) (4) 2-ct sample carton label [REDACTED] (b) (4) 1-dose powder packet label (used for 14-ct and 2-ct packages)		
<b>REVIEWER:</b>	Reynold Tan		
<b>TEAM LEADER:</b>	Marina Chang		
<b>PROJECT MANAGER:</b>	Mary Vienna		

**Background:**

This addendum applies to label comments and recommendations made in a December 2, 2008 “labeling day” meeting. This addendum adds three additional recommendations for label revision and retracts a recommendation regarding the “sodium-restricted diet” warning.

**Reviewer’s Comments:**

1. Sodium Bicarbonate: Purpose

A 11/25/08 label review stated that the purpose statement for sodium bicarbonate (e.g., “Assists in the absorption of omeprazole”) would be further discussed at a “labeling day.” During the 12/2/08 labeling day, suggestions for alternatives included “Permits absorption of this omeprazole product” and “Prevents breakdown of this omeprazole product.” These statements were preferred because either of these statements specifies that the function of sodium bicarbonate in Zegerid is specific to that product, not omeprazole-containing drugs in general. The word “Permits” was preferred over “Assists” because the latter word is associated with the

function of an excipient, which does not accurately describe sodium bicarbonate's function in Zegerid OTC. We decided to recommend that the sponsor develop an improved statement of purpose for sodium bicarbonate, while offering the two alternative statements as suggestions.

## 2. Sodium-restricted Diet Warning

The 11/25/08 label review recommended changing the "Ask a doctor before use if you have a sodium-restricted diet" warning to a "Do not use if you have a sodium-restricted diet" warning. Regulations in 21 CFR 201.64(c) require that OTC drugs containing greater than 140 milligrams of sodium be labeled "Ask a doctor before use if you have a sodium-restricted diet." Therefore, this addendum is retracting the recommendation made in the 11/25/08 label review because it does not comply with regulations. The sponsor's proposed sodium-restricted warning is acceptable.

## 3. Contraindication for Asian subpopulation

The addition of an "Ask a doctor or pharmacist before use if you are of Asian descent" warning was discussed during the 12/2/08 labeling day. The current prescription label states that "an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians." The clinical reviewer suggested that this statement be addressed in a warning statement added to the "Drug Facts" label. The warning was considered problematic because consumer interpretation of "Asian descent" would be questionable and variable. Also, the warning does not clarify what a doctor or pharmacist should do if asked about the warning. The sponsor will need to provide data to address a safety concern with use in the Asian subpopulation and/or propose labeling to reflect this warning.

## 4. Directions to take Zegerid OTC 1-hour before eating in the morning

At the 12/2/08 labeling day, the clinical pharmacology reviewer recommended revising the direction [REDACTED] (b) (4) to read "product should be taken in the morning 1-hour before eating." The revision reflects bioequivalence fed-study results, which show that the  $C_{max}$  and AUC of plasma omeprazole are significantly decreased when prescription Zegerid IR 40 mg capsules are taken 1-hour post-meal compared to being taken 1-hour pre-meal. Revised labeling must incorporate this revised warning.

### **Reviewer's Recommendations:**

In addition to the labeling recommendations in the 11/25/08 label review, the following revisions will need to be added to the action letter:

#### 1. Sodium Bicarbonate: Purpose

The agency will not accept the proposed term [REDACTED] (b) (4) as the purpose statement for sodium bicarbonate. The purpose statement should be sufficiently descriptive to enable the average consumer to understand the unique function of sodium bicarbonate in Zegerid OTC (e.g., "Permits absorption of this omeprazole product" or "Prevents breakdown of this omeprazole product").

#### 2. Contraindication for Asian subpopulation

Provide data to address a safety concern with use in the Asian subpopulation and/or propose labeling to address this safety concern. The current prescription label states that “an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians.”

3. Directions to take Zegerid OTC 1-hour before eating in the morning

Revise the direction [REDACTED] (b) (4) to read “product should be taken in the morning 1-hour before eating.” The revision reflects bioequivalence fed-study results, which show that  $C_{max}$  and AUC of plasma omeprazole are significantly decreased when prescription Zegerid IR 40mg capsules are taken 1-hour post-meal compared to being taken 1-hour pre-meal.

Note to Project Manager: Please do not send the sponsor the prototype Drug Facts label in the 11/25/08 label review. We do not want the sponsor to consider some of the language in the prototype Drug Facts (i.e., the sodium bicarbonate purpose statement, the contraindication warning for Asians) as required label statements. The sponsor should consider these statements as suggestions for revision.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Reynold Tan  
12/4/2008 08:46:53 AM  
INTERDISCIPLINARY

Marina Chang  
12/4/2008 09:21:20 AM  
INTERDISCIPLINARY



## OTC Drug Labeling Review for Zegerid OTC Powder for Oral Suspension

Division of Nonprescription Regulation Development • Office of Nonprescription Products  
Center for Drug Evaluation and Research • Food and Drug Administration

<b>SUBMISSION DATE:</b>	April 24, 2008	<b>RECEIVED DATE:</b>	April 28, 2008
<b>REVIEW DATE:</b>	November 24, 2008		
<b>NDA/SUBMISSION TYPE:</b>	NDA 22-283/N-000 (BL)		
<b>SPONSOR:</b>	Schering-Plough HealthCare Products, Inc. William Cochrane Sr. Manager, Regulatory Affairs (908)473-1858		
<b>DRUG PRODUCT(S):</b>	Zegerid OTC Powder for Oral Suspension		
<b>ACTIVE INGREDIENT (PHARMACOLOGICAL CATEGORY):</b>	omeprazole (acid reducer) sodium bicarbonate (assists in the absorption of omeprazole)		
<b>LABELING SUBMITTED:</b>	14-ct carton label (b) (4) 2-ct sample carton label (b) (4) 1-dose powder packet label (used for 14-ct and 2-ct packages)		
<b>REVIEWER:</b>	Reynold Tan		
<b>TEAM LEADER:</b>	Marina Chang		
<b>PROJECT MANAGER:</b>	Mary Vienna		

### Background:

The sponsor submitted draft labels as part of its prescription-to-OTC switch NDA application for Zegerid OTC Powder for Oral Suspension. These proposed draft labels are similar to the approved "Drug Facts" labels for Prilosec OTC delayed release tablets (NDA 21-229, approved June 20, 2003). Prilosec OTC contains 20 mg of omeprazole, but protection of omeprazole from stomach acid degradation is accomplished with a tablet coating, whereas Zegerid OTC contains sodium bicarbonate to protect omeprazole from stomach acid degradation.

The prescription Zegerid powder for oral suspension product (NDA 21-636) was approved on June 15, 2004. The approved prescription product contains either 20 mg or 40 mg omeprazole and 1680 mg of sodium bicarbonate.

## **Reviewer's Comments:**

### I. General Comments for All Labels and Package Inserts

1. The appearance of the tradename "Zegerid OTC<sub>TM</sub>" often shows "OTC<sub>TM</sub>" appearing below "Zegerid." The full tradename "Zegerid OTC<sub>TM</sub>" should appear on the same line, rather than having "OTC<sub>TM</sub>" appear below "Zegerid."
2. The purpose/pharmaceutical category of sodium bicarbonate is listed as (b) (4) on principal display panels and in the "Active Ingredients" sections of "Drug Facts." This reviewer is recommending the purpose/pharmaceutical category be changed from (b) (4) to something such as "to assist in the absorption of omeprazole," as recommended in an IND Letter to the sponsor dated April 20, 2007. The final decision as to how to label the purpose/pharmaceutical category of sodium bicarbonate needs to be discussed in a "labeling day" to obtain consensus from team members and management.

### II. Carton Labels

#### A. Principal Display Panels

1. The "NEW" banner must be removed within six months after introduction into the marketplace.
2. The term (b) (4) must be removed because this dosage strength will still be available as a prescription product for non-OTC indications.

#### B. "Drug Facts" Labels

1. Under "Use," revise the second bulleted statement by inserting a period after "heartburn" and capitalizing the "t" in "this drug...", because the statement "this drug may take 1 to 4 days for full effect" is a complete sentence.
2. Under "Ask a doctor before use if you have," the last bulleted statement reads, "a sodium-restricted diet." Move the "a sodium-restricted diet" statement from the "Ask a doctor before use if you have" section to the "Do not use if you have" section.

*Comment:* Consumers on a sodium-restricted diet should not use this product because of the high sodium content.

3. Under "Ask a doctor or pharmacist before use if you are," add the bulleted statement "of Asian descent" and, under the bulleted list of contraindicated drugs, add "clarythromycin (antibiotic)."

*Comment:* The clinical safety review for this product recommends adding these statements to the "Ask a doctor or pharmacist before use" section because the prescription label for this product states that AUC can be four times greater for Asians and that use with clarythromycin is contraindicated. However, the warning for the Asian population will require further discussion in a "labeling day" to determine how to craft a warning in a manner that will enable doctors and pharmacists to respond appropriately if asked about the warning.

4. Under “Directions,” instructions say to “empty packet contents into a small cup containing 2 tablespoons of WATER.” Consumers’ estimations of 2 tablespoons will likely be inconsistent and often inaccurate. Directions to use enough water to adequately suspend the product are sufficient.

*Comment:* Under “Directions,” this reviewer proposes changing the statement “empty packet contents into a small cup containing 2 tablespoons of WATER” to “empty packet contents into a small cup of WATER.” Language to best convey directions for taking this product will be further discussed in a “labeling day.”

5. Under “Questions,” we encourage the inclusion of the days and times when someone is available to answer phone calls next to the toll-free number.

6. The 2-ct sample carton label does not have a Drug Facts panel. (b) (4)

*Comment:* Section 502(c) of the Federal Food, Drug, and Cosmetic Act specifies that “any word, statement, or other information required by or under authority of the Act...[must be] likely to be read and understood by the ordinary individual under customary conditions of purchase and use.” The CDER Office of Compliance interprets this section of the Act to mean that the Drug Facts panel must be apparent on the outside container of all nonprescription drug products.

7. *Comment:* The font specifications for the “Drug Facts” label are acceptable for the submitted labels.

### III. 1-Dose Powder Packet Label

1. The words (b) (4) appear on the 1-dose powder packet label, even though this label only contains select (b) (4) information and does not contain the title (b) (4). Also, no space is evident for showing the product lot number or expiration date.

*Comment:* On the 1-dose powder packet label, remove the words (b) (4). If the title (b) (4) appears on a label, the label must comply with the full format and content requirements in (b) (4).

Provide space for printing the lot (or control) number and the expiration date as required in 21 CFR 201.10(i)(1).

### **Reviewer’s Recommendations:**

We are deferring communicating label recommendations until the bioequivalence and clinical issues with this product are resolved. Inform the sponsor that this application cannot be approved. Our preliminary recommendations for label changes are as follows:

#### I. A General Comment for All Labels and Package Inserts

1. Present the full tradename “Zegerid OTC<sub>TM</sub>” on the same line, rather than having “OTC<sub>TM</sub>” appear below “Zegerid.”

## II. Carton Labels

### A. Principal Display Panels

1. Remove the “NEW” banner within six months after introduction into the marketplace.
2. Remove the term [REDACTED] (b) (4) because this dosage strength will still be available as a prescription product for non-OTC indications.

### B. Drug Facts Labels

1. Under “Use,” revise the second bulleted statement by inserting a period after “heartburn” and capitalizing the “t” in “this drug may take 1 to 4 days for full effect.”
2. Move the “sodium-restricted diet” statement from the “Ask a doctor before use if you have” section to the “Do not use if you have” section.
3. Under “Ask a doctor or pharmacist before use if you are,” add “clarythromycin (antibiotic)” to the bulleted list of contraindicated drugs.
4. Under “Questions,” we encourage the inclusion of the days and times when someone is available to answer phone calls next to the toll-free number.
5. Include a Drug Facts panel on the 2-ct sample carton label as required by Section 502(c) of the Federal Food, Drug, and Cosmetic Act.

## III. 1-Dose Powder Packet Label

1. Remove the words [REDACTED] (b) (4). The title [REDACTED] (b) (4) applies strictly to labels that comply in full with [REDACTED] (b) (4) format and content requirements in [REDACTED] (b) (4).
2. Provide space for printing the lot (or control) number and the expiration date as required in 21 CFR 201.10(i)(1).

IV. “Labeling day” Discussion. The following items need to be discussed further in a “labeling day” before recommendations for revision are communicated to the sponsor:

- A. This review proposes changing the purpose/pharmaceutical category of sodium bicarbonate wherever it appears (e.g., “Active Ingredients” section of the “Drug Facts” label, principal display panels) from [REDACTED] (b) (4) to “Assists in the absorption of omeprazole.”
- B. Under “Ask a doctor or pharmacist before use if you are,” add the bulleted statement “of Asian descent.” The prescription label for this product states that AUC can be four times greater for Asians. However, this warning will require further discussion to determine how to craft a warning in a manner that will enable doctors and pharmacists to respond appropriately if asked about the warning.
- C. Under “Directions,” instructions to “empty packet contents into a small cup containing 2 tablespoons of WATER” may need revision because consumers’ estimations of 2 tablespoons will likely be inconsistent and often inaccurate. This reviewer proposes changing the statement

to simply “empty packet contents into a small cup of WATER.” However, language to best convey directions for taking this product will be further discussed.

V. Note to Project Manager:

- A. Inform the sponsor further revisions of the labels may be required after all reviews have been completed.
- B. Do not provide preliminary review to the sponsor before “labeling day” discussions.
- C. Please provide the attached prototype “Drug Facts” label for the sponsor to use as a guide for their preliminary revisions. Further revisions may be necessary pending completion of the NDA review.

Attachment: “Drug Facts” label - prototype

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Reynold Tan  
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Marina Chang  
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INTERDISCIPLINARY



## SOCIAL SCIENCE REVIEW

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Food and Drugs Administration  
Center for Drug Evaluation and Research  
**Office of Nonprescription Products**

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**NDA:** 22-281 and 22-283

**Type of Submission:** New NDA

**Product/Ingredient Name:**

Zegerid (omeprazole/sodium bicarbonate) OTC™ capsule (NDA 22-281)

Zegerid (omeprazole/sodium bicarbonate) OTC™ powder (NDA 22-283)

**Dosage Form Route of Administration:** oral

**Sponsor:** Schering-Plough Healthcare Products

**Date Submitted:** March 10, 2008

**Date Received:** April 25, 2008

**Date Review Completed:** September , 2008

**Reviewer:** Laura Shay, RN, MS, C-ANP, Social Science Analyst

**Introduction**

This document is a review of the Zegerid OTC™ Use & Directions study # 234 conducted in support of NDA 22-281 and 22-283, and the review of Zegerid OTC™ Use Directions Targeted Label Study #237 conducted in support of NDA 22-283.

**Background**

Zegerid (omeprazole/sodium bicarbonate) is a proton-pump inhibitor. Prescription Zegerid® 20 mg powder for oral suspension was approved in June 2004 (NDA 21-636). Zegerid® 20 mg and 40 mg capsules were approved in February, 2006 (NDA 21-849). Discussions with the Agency on an Rx-to OTC switch began in September, 2005 with Santarus, Inc. In 2006, Schering-Plough HealthCare Products (SPHCP) entered into an agreement with Santarus to develop Zegerid products for OTC use.

SPHCP first met with FDA on February 7, 2007 to discuss their development plan for nonprescription Zegerid® (omeprazole 20 mg and sodium bicarbonate 1680 mg). SPCHP was told that they would need to provide a pharmacokinetic (PK) study that compares the bioavailability of their product to Prilosec OTC® and if the PK parameters fall outside the bioequivalence criteria, they would need to provide additional data to support safety and efficacy of Zegerid. In addition, SPHCP was told that because the action of the sodium bicarbonate contained in Zegerid® is only to enhance the absorption of the omeprazole and not to reduce acid they may need to demonstrate that consumers understand that the function of the sodium bicarbonate is not to provide heartburn relief.

On July 18, 2007, the Agency sent SPHCP an Advice Letter which conveyed the following:

- If SPHCP is successful in bridging their product to Prilosec OTC through PK data, the data will not support a claim in labeling or advertising suggesting that your product is better than Prilosec OTC. Labeling implying an immediate effect will not be acceptable.
- 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”.

- To assure consumers will not be confused about the use of this product and the function of the sodium bicarbonate, SPHCP may be required to provide a label comprehension study and possibly consumer behavior studies to demonstrate consumers will use the product correctly.
- The product should contain the sodium labeling if it falls within the criteria listed in 21 CFR 201.64.
- Because consumers will be exposed to daily dose of sodium bicarbonate, SPHCP will need to include any warnings that are applicable to sodium bicarbonate
- Because the proposed 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. SPHCP will need to identify any potential safety issues included in the current prescription labeling or new safety issues after review of the safety database and determine how they should be addressed by OTC labeling.

On October 30, 2007 a second meeting was held with SPHCP. As part of the background package for this meeting SPCHP submitted a draft label and the results from a label comprehension study #234. The study evaluated consumer comprehension of product use and directions for the capsule, and the understanding of the proposed statements describing the purpose of the sodium bicarbonate ingredient. The study compared three different versions of the Zegerid label plus a comparator (Prilosec OTC) label. SPHCP summarized that the label options tested performed strongly on all key communication objectives and scored equal to or higher than the Prilosec OTC® label. The Zegerid® OTC (b) (4) label best communicated the purpose of sodium bicarbonate (correct/acceptable: general population 85%; 79% low literacy). The (b) (4) label also communicated this objective “solidly” (correct/acceptable: general population 63%; 56% low literacy) and better than the (b) (4) label (correct/acceptable: general population 36%; 41% low literacy). Although the “absorption enhancer” label did not have the highest comprehension scores (correct/acceptable: general population 63%; 56% low literacy) SPHCP felt that the scores were “solid” and proposed to use the language “absorption enhancer” to describe the purpose of sodium bicarbonate. Comprehension of the directions for use of the powdered form was not tested.

The Agency did not concur with SPHCP’s summary analysis. Comprehension scores ranging from 56-63% do not represent “solid” understanding. SPHCP was told that they should come up with new descriptor(s) for sodium bicarbonate and conduct a targeted label comprehension study to test consumer understanding of the new descriptor(s). It was also conveyed to SPHCP that the word (b) (4) may imply added benefit. In addition, they were told that they should test the 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.

On December 5, 2007 SPHCP submitted a proposed study protocol for a targeted label comprehension study to test understanding of the directions for use of the powered form of Zegerid OTC. In the cover letter, SPHCP states that they have chosen not to pursue the (b) (4) descriptor for sodium bicarbonate. Based on their results from the previous label comprehension study SPHCP has decided to use the term (b) (4) which they feel tested well (correct/acceptable: general population 85%; 79% low literacy). In addition, SPHCP states that the term (b) (4) is similar to that used to describe (b) (4). Comments on the study design were sent to SPHCP on February 6, 2008. Comments concerning whether or not (b) (4) can be used as the descriptor for sodium

bicarbonate were deferred until a full review of the study results were completed at the time of the NDA submission.

On March 10, 2008, SPHCP submitted NDA 22-281 (Zegerid OTC™ capsule) and NDA 22-283 (Zegerid OTC™ powder). Results of two label comprehension studies were included in the submission. The following is a review of the Zegerid OTC™ Use & Directions study # 234 conducted in support of NDA 22-281 and 22-283, and the review of Zegerid OTC™ Use Directions Targeted Label Study #237 conducted in support of NDA 22-283

## Reviews

### I. Study Title: Zegerid OTC™ Use & Directions study # 234

**Purpose:** To evaluate consumer comprehension related to product use and directions based on three proposed Principal Display Panels and Drug Facts labels for Zegerid® OTC and an active control (Prilosec OTC™).

**Study Design:** Four group (cell), random assignment-multi center descriptive design.

**Objectives:** Able to understand the following communication objectives

#### Primary:

- The purpose of sodium bicarbonate [REDACTED] (b) (4)
- Product not to be used if taking a prescription drug unless checking with a physician
- If on low sodium diet, check with a doctor before use
- Not to be taken for more than once a day
- Product treats frequent heartburn
- Product is not for immediate relief
- It may take one to four days to take effect
- It is to be taken every day for 14 days

#### Secondary:

- The course of therapy may be repeated every four months
- Product is to be used only once a day
- When taking, one pill is to be swallowed accompanied by a glass of water
- It is not to be chewed
- It is not to be sprinkled
- It is not to be used for more than 14 days without checking with a physician
- It is not to be taken by children under 18 unless a doctor approves

## Study Sample:

Cohort 1 (Representative Cohort): Adult self-reported sufferers of heartburn-general population (both normal literacy and low literacy)

Cohort 2 : Low literacy cohort (Rapid Estimate of Adult Literacy in Medicine (REALM) scores of 60 or below which equals at or below an 8<sup>th</sup> grade reading level).

Representative population cohorts in each cell were roughly balanced in the following way so not to introduce bias:

- Approximately 50% women; 50% men
- The same ages, within the ranges of 18 to 34, 35 to 54, and 55 and older

- The same percentage who has used an antacid in the past three months
- The same percentage who has used Prilosec OTC in the past three months
- The same percentage who suffer from heartburn one day a week or less
- The same percentage who suffer form heartburn two or more days a week

Reviewer’s comment

*It is unclear what “The same ages, within the ranges of 18 to 34, 35 to 54, and 55 and older” means. Most likely it is an error and the Sponsor meant to say “The same number of subjects within the ranges of 18 to 34, 35 to 54, and 55 and older.”*

Four cells consisted of 4 different labels tested:

1. Zegerid™ OTC (b) (4) (n=403)
2. Zegerid™ OTC (b) (4) (n=397)
3. Zegerid™ OTC (b) (4) (n=407)
4. Prilosec OTC™ (n=409)

The key difference between the three Zegerid labels is the way in which sodium bicarbonate ingredient is described: (b) (4) Prilosec OTC™ does not contain sodium bicarbonate therefore a descriptor for sodium bicarbonate is not included on the label.

**Sample Size Justification:**

The base of 400 interviews per cohort provides a point estimate of +/-5% at the 95% Confidence Interval (CI) in the worst case situation (i.e., 50%); the base of 150 interviews with a low literate cohort per cell provides at least +/- 8% in the same situation. If questions are answered correctly by 80% or higher, the 95% CI becomes +/-4% for the Representative Cohort per cell and +/- 6.6% for the Low Literate Cohort per cell. If 90% answer correctly, the CI is +/- 3% for the Representative Cohort per cell and +/-4.9% for the Low Literate Cohort per cell.

**Study sites:** Multi-center study. Respondents were recruited from 55 geographically dispersed shopping malls sited across the U.S.

<b>CITY:</b>	(12)	<b>CITY:</b>	(14)	<b>CITY:</b>	(13)
Albany (b) (4)	- 1	Huntington (b) (4)	- 1	Pittsburgh (b) (4)	- 1
Appleton (b) (4)	- 2	Indianapolis (b) (4)	- 2	Pittsburgh (b) (4)	- 2
Atlanta (b) (4)	- 3	Jackson (b) (4)	- 3	Portland (b) (4)	- 3
Atlanta (b) (4)	- 4	Kansas City (b) (4)	- 4	Providence (b) (4)	- 4
Boston (b) (4)	- 5	Kansas City (b) (4)	- 5	Puyallup (b) (4)	- 5
Boston (b) (4)	- 6	Knoxville (b) (4)	- 6	Sacramento (b) (4)	- 6
Boynton Beach (b) (4)	- 7	Los Angeles (b) (4)	- 7	Salt Lake City (b) (4)	- 7
Charlotte (b) (4)	- 8	Memphis (b) (4)	- 8	San Diego (b) (4)	- 8
Colorado Springs (b) (4)	- 9	Miami (b) (4)	- 9	San Diego (b) (4)	- 9
Denver (b) (4)	- 0	Milwaukee (b) (4)	- 0	San Francisco (b) (4)	- 0
	(13)		(15)		(14)
Denver (b) (4)	- 1	Minneapolis (b) (4)	- 1	Seattle (b) (4)	- 1
Detroit (b) (4)	- 2	Montgomery, AL (b) (4)	- 2	St. Louis (b) (4)	- 2
Detroit (b) (4)	- 3	Nashville (b) (4)	- 3	Tallahassee (b) (4)	- 3
Durham (b) (4)	- 4	New York (b) (4)	- 4	Tampa (b) (4)	- 4
Eau Claire (b) (4)	- 5	New York (b) (4)	- 5	Tulsa (b) (4)	- 5
Erie (b) (4)	- 6	Oklahoma City (b) (4)	- 6		
Ft. Smith (b) (4)	- 7	Omaha (b) (4)	- 7		
Hartford (b) (4)	- 8	Philadelphia (b) (4)	- 8		
Houston (b) (4)	- 9	Phoenix (b) (4)	- 9		
Houston (b) (4)	- 0	Phoenix (b) (4)	- 0		

### **Inclusion Criteria**

- Age 18 years or older
- Have suffered heartburn at least once in the past 30 days
- Have corrective lenses available for reading
- Able to read English

### **Exclusion Criteria:**

- Have participated in any marketing research regarding health care products within the past 90 days
- Have participated in any product label or product booklet studies in the past 12 months
- Have competitive affiliation which means neither they nor anyone in their household is employed by a marketing research company, ad agency/public relations firm, a pharmacy, a pharmaceutical company, a manufacturer of medicines or healthcare items, a managed care/health insurance company, or as part of healthcare practice (e.g. receptionist at a doctor's office) or by the Food and Drug Administration
- Not know or refuse to answer how many days suffer from heartburn in a typical week
- Will unbalance the four cells (be more than needed to match cells) with respect to:
  - frequency of heartburn suffering
  - gender
  - use of antacids past 3-months
  - use of Prilosec OTC, past three months

### Reviewer's Comments

*It is unclear why only individuals who suffer heartburn at least once in the past 30 days were eligible for this study.*

**Study Description:** Potential respondents were screened on the mall and those who qualified (see inclusion/exclusion criteria) and agreed to participate were taken to a research facility located inside the mall. The main qualifying question on the screener listed a variety of health conditions in order to mask the indication for the proposed product. Those who reported having heartburn continued to be screened, those who did not were terminated from the screening process. The remaining questions were also imbedded in order to mask the product indication. Each respondent was first administered the REALM test to assess their literacy in medicine score. They were then randomly assigned to one of four labels: Three proposed versions of the Zegerid® OTC label (b) (4) and the (4) Prilosec OTC® label. Each respondent was given as much time as needed to review the package label (both the principal display panel and Drug Facts-see attached). The respondent could refer to the label at any time during the interview. Once the respondent finished reading the label, the computer assisted personal interview took place. All respondents were given a \$2.00 "thank you" for their time and willingness to co-operate.

### Reviewer's Comments

*The Sponsor submitted the screening script. The questions and the order of the questions do not pose any potential bias.*

**Data Collection:** Data was collected by a trained interviewer using the Computer Assisted Personal Interview (CAPI). All questions were randomly presented except the first question. Questions were open-ended and closed ended. Third person scenario questions were primarily used. Of the 16 questions, three concerning sodium bicarbonate did not apply to Prilosec OTC®.

A pilot study was held in one city prior to the start of interviewing in order to make certain that interviewing would be properly conducted and to make changes to the questionnaire where necessary.

### Reviewer's Comments

*The questionnaire contains 16 questions plus 19 probing questions. The questionnaire includes both open-ended and closed-ended questions. There is one question for each communication objective. None of the questions appear to be leading and are overall well written. The order of the questions are mixed and do not follow the order of the label which reduces the possibility of respondent learning. Fifteen of the questions are based on scenarios followed by probing questions. The probing question "why do you say that?" is only asked to respondents who incorrectly answer a question. Ten of the scenario based questions ask participants' if it is "ok" or "not ok" for the person to use Zegerid. Respondents have a 50% chance of selecting the correct answer. Because respondents who answer these questions correctly are not asked why they answered the way they did, there is no validation that their response is truly correct versus correct based on 'guessing'. Therefore, without validation, it is difficult to interpret the reliability of the study findings.*

*The question designed to assess if respondents understand the purpose of sodium bicarbonate is the following: "According to the label, what if anything, does sodium bicarbonate have to do with this product?" Respondents' who answered the following are coded as being correct:*

(b) (4)  


*These answers are simply the descriptors of sodium bicarbonate provided on each of the three label variations. Because there is no probing question that asks respondents what they think those statements mean, it is unknown if respondent's understand the purpose of sodium bicarbonate based on those descriptors.*

### **Analysis:**

For the first three primary objectives that deal with sodium bicarbonate, the evaluation method is to select the Zegerid OTC label option that is best comprehended. For the remaining objectives and the Secondary objectives the evaluation method is to determine if the percentage of accurate responses based on each of the three Zegerid OTC labels is higher, the same as, or lower than the percentage of accurate responses based on the Prilosec OTC label.

The Sponsor described the following "Net Coding Process" for correct, acceptable or incorrect answers:

An answer was considered "correct" if the initial response showed a clear understanding of the point of the question. Such responses were pre listed on the questionnaire, and any respondent providing a correct answer was moved automatically to the next question. An "acceptable" answer was one where the initial response was incorrect or ambiguous, and the respondent gave the correct answer when probed. These include respondents who changed their minds upon reflection, and those who clarify when probed. Generally, the response "ask a doctor" was considered incorrect, as that response can be a default. However, for the objectives where "ask a doctor" is the suggested action on the label, responses are coded as "correct" if respondent provides that response initially and coded as "acceptable" if respondent provides an unclear response initially but responds "ask a doctor" when probed. Other incorrect answers were those where the respondent answered clearly but incorrectly.

The Sponsor included the coding procedures for open-ended questions submitted “Professional Coding Quality Controls”.

Analysis of Variance followed by post hoc testing was used when a comparison between labels was appropriate. If overall testing between cells was significant ( $p \leq .05$ ), Dunnett’s procedure was used to determine whether or not each Zegerid OTC label cell differed from the Prilosec OTC “active control” while keeping the overall significance level for all tests set at  $p \leq .05$ .

Reviewer’s Comments

The coding procedures are well described and follow standard procedure.

**Results:**

SPHCP reported that a total of 1,913 respondents were interviewed. The demographics make up of the samples are presented in Tables 1-6.

**Table 1 Number in Representative and Low Literacy Samples by Cell and in Total**

Category	(b) (4)			Prilosec OTC	Total
	Representative Sample	403	397	407	
Low Lit. Sample	151	155	153	155	614
Low Literacy in Both Rep and Low Literacy Samples	76	80	77	84	317
Percent of Low Literacy in Representative	19%	20%	19%	21%	20%

**Table 2 Gender Representative Sample/Low Literate Sample**

QK. Gender	A. Representative Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
Male	202 50%	195 49%	204 50%	202 49%
Female	201 50%	202 51%	203 50%	207 51%

QK. Gender	B. Low Literacy Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
Male	82 54%	80 52%	83 54%	86 56%
Female	69 46%	75 48%	70 46%	69 45%

**Table 3 Age Representative Sample/Low Literate Sample**

QF. Age	A. Representative Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
18-34	153 38%	148 37%	148 36%	155 38%
35-54	154 38%	155 39%	161 40%	156 38%
55+	96 24%	94 24%	98 24%	98 24%
<b>Mean (#)</b>	<b>40.57</b>	<b>41.07</b>	<b>41.38</b>	<b>40.46</b>

QF. Age	B. Low Literacy Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
18-34	80 53%	63 41%	59 39%	68 44%
35-54	44 29%	62 40%	62 41%	57 37%
55+	27 18%	30 19%	32 21%	30 19%
<b>Mean (#)</b>	<b>36.75</b>	<b>39.41</b>	<b>39.90</b>	<b>38.34</b>

**Table 4 Frequency of Heartburn Representative Sample/Low Literate Sample**

QB3 Frequency of Heartburn in typical week	A. Representative Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
One day a week or less	155 39%	147 37%	150 37%	156 38%
Two or more days a week	248 62%	250 63%	257 63%	253 62%
<b>Mean (#)</b>	<b>2.44</b>	<b>2.62</b>	<b>2.65</b>	<b>2.58</b>

QB3 Frequency of Heartburn in typical week	B. Low Literacy Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
One day a week or less	49 33%	53 34%	44 29%	50 32%
Two or more days a week	49 68%	53 66%	44 71%	50 68%
<b>Mean (#)</b>	<b>2.44</b>	<b>2.61</b>	<b>2.59</b>	<b>2.67</b>

**Table 5 REALM Score Representative Sample/Low Literate Sample**

QJ REALM Test Score	A. Representative Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
0-20	9 2%	15 4%	8 2%	9 2%
21-40	9 2%	11 3%	7 2%	9 2%
41-60	58 14%	54 14%	62 15%	66 16%
61+	327 81%	317 80%	330 81%	325 79%
<b>Mean (#)</b>	<b>61.57</b>	<b>60.47</b>	<b>61.73</b>	<b>61.15</b>

QJ REALM Test Score	B. Low Literacy Cohort Cells			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
0-20	9 6%	17 11%	8 5%	9 6%
21-40	16 11%	15 10%	10 7%	14 9%
41-60	126 83%	123 79%	135 88%	132 85%
61+	0 0%	0 0%	0 0%	0 0%
<b>Mean (#)</b>	<b>50.34</b>	<b>47.84</b>	<b>51.51</b>	<b>50.32</b>

**Table 6 Prilosec OTC Use Representative Sample/Low Literate Sample**

	(b) (4)			Prilosec OTC
<b>Representative</b>	34(8%)	38 (10%)	37 (9%)	35(9%)
<b>Low literate</b>	9(6%)	16(10%)	12(8%)	15(10%)

Reviewer’s Comments

The demographic makeup of all cells appear to be equally distributed based on age, gender, frequency of heartburn suffering, and use of Prilosec OTC. Based on the REALM scores across cells the majority of the low literacy sample had scores of 41-60 which is equivalent to a 5<sup>th</sup>-8<sup>th</sup> grade reading level.

The following are summary of the results tables (Table 7-Table 10) provided by the Sponsor. Each table describes the proportion of respondents in the Representative sample and the low literate sample who gave either a “correct” or “acceptable” answer to each question associated with the primary and secondary study objectives: The columns are lettered A,B,C within the Representative Cohort and D,E,F within the Low Literacy Cohort and significance at the p=.05 significance level is indicated by placing a capital letter next to the highest cell percentage. This indicates it is statistically significantly higher than the percentage in the lettered column, same row at p≤ .05.

**Table 7 Summary of Primary Communication Objective Findings-Representative Cohort**

	<b>A. Representative Cohort</b>			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
	A	B	C	D
<b>Primary Communication Objectives</b>				
P1. The purpose of sodium bicarbonate – (b) (4)				
	(b) (4)			
<b>Correct/Acceptable</b>	341 85%BC	143 36%	256 63%B	NA
P2. Product is not to be used if taking a prescription drug without checking with physician. <b>Correct/Acceptable</b>	318 79%	301 76%	315 77%	NA
P3. If on a low sodium diet, check with a doctor before use. <b>Correct/Acceptable</b>	374 93%	363 91%	366 90%	NA
P4. It is not to be taken more than once a day. <b>Correct/Acceptable</b>	337 84%	344 87%	366 90%D	342 84%
P5. Product treats frequent heartburn. <b>Correct/Acceptable</b>	370 92%	365 92%	371 91%	376 92%
P6. Product is not for immediate relief. <b>Correct/Acceptable</b>	277 69%	269 68%	307 75%	282 69%
P7. It may take one to four days to take effect. <b>Correct/Acceptable</b>	371 92%	381 96%	383 94%	384 94%
P8. It is to be taken every day for 14 days. <b>Correct/Acceptable</b>	332 82%	346 87%	371 91%D	342 84%

NA = Not Applicable. Letters = significantly higher than percent in letter column, same row ( $p \leq .05$ ).

**Table 8 Summary of Primary Communication Objective Findings-Low Literacy Cohort**

	<b>B. Low Literacy Cohort</b>			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
	A	B	C	D
<b>Primary Communication Objectives</b>				
P1. The purpose of sodium bicarbonate – (b) (4)				
	(b) (4)			
<b>Correct/Acceptable</b>	120 79%BC	63 41%	86 56%B	NA
P2. Product is not to be used if taking a prescription drug without checking with physician. <b>Correct/Acceptable</b>	130 86%	122 79%	131 86%	NA
P3. If on a low sodium diet, check with a doctor before use. <b>Correct/Acceptable</b>	145 96%	144 93%	143 94%	NA
P4. It is not to be taken more than once a day. <b>Correct/Acceptable</b>	129 85%	129 83%	136 89%	128 83%
P5. Product treats frequent heartburn. <b>Correct/Acceptable</b>	138 91%	136 88%	145 95%	139 90%
P6. Product is not for immediate relief. <b>Correct/Acceptable</b>	107 71%	88 57%	108 71%	95 61%
P7. It may take one to four days to take effect. <b>Correct/Acceptable</b>	138 91%	145 94%	141 92%	147 95%
P8. It is to be taken every day for 14 days. <b>Correct/Acceptable</b>	127 84%	131 85%	132 86%	126 81%

NA = Not Applicable. Letters = significantly higher than percent in letter column, same row ( $p \leq .05$ ).

**Table 9 Summary of Secondary Communication Objective Findings- Representative Cohort**

	<b>A. Representative Cohort</b>			
	(b) (4)			Prilosec OTC
<b>Rep. Base – total per group</b>	<b>403</b>	<b>397</b>	<b>407</b>	<b>409</b>
	#	#	#	#
	%	%	%	%
<b>Secondary Communication Objectives</b>				
S1. The course of therapy may be repeated every four months. <b>Correct/Acceptable</b>	313 78%	316 80%	329 81%	303 74%
S2. Product is to be used only once a day. – John Scenario <b>Correct/Acceptable</b>	359 89%	362 91%	361 89%	367 90%
S2. Product is to be used only once a day. – Direct <b>Correct/Acceptable</b>	391 97%	383 96%	397 98%	387 95%
S3. When taking, one pill is to be swallowed (accompanied by a glass of water). <b>Correct/Acceptable</b>	390 97%	387 97%	400 98%	389 95%
S4. It is not to be chewed. <b>Correct/Acceptable</b>	357 89%	351 88%	356 87%	346 85%
S5. It is not to be sprinkled. <b>Correct/Acceptable</b>	340 84%	329 83%	356 87%	347 85%
S6. It is not to be used for more than 14 days without checking with physician. <b>Correct/Acceptable</b>	328 81%	311 78%	336 83%	325 79%
S7. Product is not to be taken by children under 18 unless a doctor approves. <b>Correct/Acceptable</b>	368 91%	356 90%	370 91%	370 90%

**Table 10 Summary of Secondary Communication Objective Findings- Low Literacy Cohort**

	<b>B. Low Literacy Cohort</b>			
	(b) (4)			Prilosec OTC
<b>Low Lit. Base – total per group</b>	<b>151</b>	<b>155</b>	<b>153</b>	<b>155</b>
	#	#	#	#
	%	%	%	%
<b>Secondary Communication Objectives</b>				
S1. The course of therapy may be repeated every four months. <b>Correct/Acceptable</b>	124 82%	114 74%	119 78%	112 72%
S2. Product is to be used only once a day. – John Scenario <b>Correct/Acceptable</b>	135 89%	134 86%	136 89%	135 87%
S2. Product is to be used only once a day. – Direct <b>Correct/Acceptable</b>	143 95%	145 94%	147 96%	142 92%
S3. When taking, one pill is to be swallowed (accompanied by a glass of water). <b>Correct/Acceptable</b>	147 97%	150 97%	148 97%	143 92%
S4. It is not to be chewed. <b>Correct/Acceptable</b>	133 88%	131 85%	134 88%	127 82%
S5. It is not to be sprinkled. <b>Correct/Acceptable</b>	136 90%	125 81%	129 84%	129 83%
S6. It is not to be used for more than 14 days without checking with physician. <b>Correct/Acceptable</b>	127 84%	117 75%	119 78%	126 81%
S7. Product is not to be taken by children under 18 unless a doctor approves. <b>Correct/Acceptable</b>	136 90%	138 89%	137 90%	140 90%

### Reviewer's Comments

The Sponsor has chosen the label that contains (b) (4) to describe sodium bicarbonate; therefore the comments will only address the results from the (b) (4) cohorts.

The results demonstrate that 85% of the Representative Cohort and 79% of the Low Literate Cohort were able to read the descriptor (b) (4). These results do not provide data to support the primary objective of the study that the participants were able to understand the purpose of sodium bicarbonate. Those who answered Question 3 ("According to the label, what if anything, does sodium bicarbonate have to do with this product?") (b) (4) were considered 'correct' and were not asked the probing "why do you say that?" Therefore, it is unknown if these participants understood the purpose of sodium bicarbonate.

The Drug Facts Label for Zegerid OTC contains the same warnings and directions listed on the currently marketed Prilosec OTC label. The Prilosec OTC label was tested for comprehension prior to approval. The warnings that are different on the Zegerid label are related to the sodium bicarbonate. These include: "each capsule contains sodium (b) (4)", "Ask a doctor before use if you have a sodium-restricted diet", "Ask a doctor or pharmacist before use if you are taking tacrolimus (immune system medicine), atazanavir (anti-viral medicine), any other prescription drugs. Sodium bicarbonate may interact with certain prescription drugs." Because Zegerid OTC is a capsule rather than a tablet the statement "do not open capsule and sprinkle on food" is added to the directions for use. The range of correct/acceptable answers to the questions related to these communication elements were 79-93% for the Representative Cohort and 86-96% for the Low Literate Cohort. Interestingly the Low Literate Cohort tested higher. The remaining label elements tested are identical to those found on the current Prilosec OTC label. Both the Representative Cohort the Low Literate Cohort tested  $\geq 78\%$  for all questions related to directions and warnings with both cohorts testing as well as and sometimes better than the Prilosec OTC cohorts. The one exception where both the Prilosec OTC cohorts and the Zegerid OTC cohorts tested at  $\leq 71\%$  is the question that addresses the statement that describes the product is not for immediate relief.

As described above, because respondents who answer closed-ended questions correctly are not asked why they answered the way they did, there is no validation that their response is truly correct versus correct based 'guessing'. Therefore, without validation, it is difficult to interpret the reliability of the study findings.

### **Conclusions**

A proposal of this study was not submitted to FDA for review and comment.

The strength of the study was that it tested several versions of a label and tested a comparator. Overall the study design was inadequate because the questionnaire did not include open-ended questions to validate correct responses to closed-ended questions or used several close-ended questions to test one communication objective. Therefore, it is difficult to interpret the findings. The Sponsor has chosen to use (b) (4) as the descriptor for sodium bicarbonate. The study provided data to support that 85% of the Representative Cohort and 79% of the Low Literate respondents' were able to read this descriptor. The study did not provide data to support the primary objective of the study that the respondents were able to understand the purpose of sodium bicarbonate.

Unless the sponsor chooses to conduct a new label comprehension study that accurately assesses the ability of consumers to understand the purpose of sodium bicarbonate, sodium bicarbonate should be removed from the principle display panel (PDP). Until it is demonstrated that consumers understand that the purpose of sodium bicarbonate is to assist in the absorption of omeprazole,

listing it on the PDP potentially misleads consumers to believe that the sodium bicarbonate also treats heartburn by helping to reduce acid. This is especially true for the descriptor chosen by the Sponsor [REDACTED] (b) (4)

**Recommendations:**

1. Results from the label comprehension study only demonstrated the ability of respondents to read the verbatim descriptor the Sponsor chose for sodium bicarbonate. If the Sponsor wishes to leave sodium bicarbonate on the Principal Display Panel (PDP), they will need to conduct a new label comprehension study to assess understanding of the purpose of sodium bicarbonate. Until such time the Sponsor will need to remove sodium bicarbonate and the descriptor [REDACTED] (b) (4) from the (PDP).
2. Under ‘Active ingredient’ in Drug Facts the purpose of sodium bicarbonate should be changed from [REDACTED] (b) (4) to “helps omeprazole work.”

II. Study Title: Zegerid OTC™ Use Directions Targeted Label Study #237

**Background:**

The protocol for Study #237 is identical to the protocol submitted on December 5, 2007 requesting Agency review and comment. Comments and recommendations were sent to SPHCP on February 6, 2008. SPHCP chose to conduct the study prior to receiving comment from the Agency and therefore the protocol submitted under the NDA is the same protocol that was submitted December 5, 2007 protocol. The following is the December 2007 protocol review followed by a review of the study results.

**Objectives:** To evaluate consumer comprehension of four product use directions for the proposed Zegerid™ OTC Powder Packet label:

1. product should be emptied into small cup containing 2 tablespoons of water
2. product is not to be mixed with any other liquid
3. product is not to be mixed with any food
4. product must be stirred well
5. mixed product must be drunk immediately
6. another cup of water must be drunk after drinking mixed product

**Study Design:** One group descriptive

**Study Sample:** Frequent heartburn sufferers defined as suffering heartburn two or more days in a week, who have had at least one episode of heartburn in the past 30 days.

Two cohorts:

Cohort 1: General population of frequent heartburn sufferers (n=400)

Cohort 2: Low literate frequent heartburn sufferers: REALM score ≤ 60 (n=150)

Reviewer’s Comment

*It is not clear why respondents need to be only individuals who suffer from frequent heartburn. The directions for using the powder form of the product are not something that requires a subpopulation of potential users.*

**Study sites:** The study was conducted in 24 geographically dispersed shopping malls. See Table 1:

**Table 1: Study Sites**

CITY			
Atlanta	- 1	Los Angeles	- 13
Boston	- 2	Memphis	- 14
Boynton Beach	- 3	Mesa	- 15
Colorado Springs	- 4	Milwaukee	- 16
Denver	- 5	New York	- 17
Detroit	- 6	Oklahoma City	- 18
Durham	- 7	Omaha	- 19
Eau Claire	- 8	Puyallup	- 20
Ft. Smith	- 9	San Francisco	- 21
Houston	- 10	St. Louis	- 22
Jackson	- 11	Tampa	- 23
Kansas City	- 12	Tulsa	- 24

**Sample Size Determination:**

Precision is defined as the distance from the target response rate at the 95% confidence interval of the proportion of respondents giving a correct or acceptable response (minimally acceptable response rate). It was determined that a sample size of 400 general population of frequent heartburn sufferers yields +/-5% at the 95% confidence interval. Testing will determine if the correct/acceptable percentage is statistically higher than the same as or lower than the 70% performance standard. A sample of 150 frequent heartburn suffers of low literacy yields +/-8% at the 95% confidence interval.

Reviewer's Comment

*Sample size determination is acceptable using a lower bound of 70%.*

**Inclusion criteria:**

1. 18 years or older
2. have suffered heartburn at least once in the past 30 days
3. typically suffer heartburn two or more days a week
4. have corrective lenses available if needed for reading
5. be able to read English
6. score below ninth grade reading level on the REALM (low literacy cohort)

**Exclusion criteria:**

1. have participated in any marketing research regarding healthcare products within the past 90 days
2. have participated in any product label or product booklet studies in the past 12 months
3. have competitive affiliation which means neither they nor anyone in their household will be employed by a marketing research company, ad agency/public relations firm, a pharmacy, a pharmaceutical company, a manufacturer of medicines or healthcare items, a managed care/health insurance company, or as part of a healthcare practice (e.g. receptionist at a doctor's office), or by the Food and Drug Administration

### Reviewer's Comment

*It is not clear by the exclusion criteria if healthcare providers such as doctors, nurses or pharmacists are excluded. A pharmacist does not necessarily need to be affiliated with a pharmacy or pharmaceutical company. Likewise a physician, physician assistant, or nurse is not necessarily affiliated with a healthcare practice.*

### **Study plan:**

After being administered the REALM test, respondents were given as much time as needed to review the package label. Once the respondent has finished reading the label, and signaled the interviewer, the interviewer administered the computer assisted personal interview. Respondents were given \$3.00 for their time.

### **Data Collection:**

Respondents were asked questions relating to each of the communication points to determine what percent in each cohort comprehend the point. The questionnaire used contained open-ended, closed ended and scenario based questions. If respondents gave an incorrect answer to an initial question, were asked a follow-up open-ended probe to understand the rationale behind their answer. The questions were presented in random order from respondent to respondent to prevent order bias.

The Sponsor provided the coding quality standards.

### Reviewer's Comments

*The Sponsor provided a copy of the questionnaire. The questionnaire contains six scenario based questions with the question "what led you to make that decision?" after each question. The Sponsor states that respondents who gave an incorrect answer to an initial question were asked a follow-up open-ended probe to understand the rationale behind their answer. Because closed-ended questions ("is it ok or not ok") allow for a correct response due to chance, it is important that the open-ended probing question also be asked to respondents who were correct in order to validate their response and eliminate those who guessed the correct answer.*

*Open-ended questions do not require validation, therefore it is appropriate to only probe respondents who answered incorrectly. Questioning respondents who were incorrect is important in order to assess why errors were made and where improvements to the label should be made.*

*To prevent bias from only focusing on the directions associated with preparing and ingesting the powder form of the product, other questions should have been mixed in that are unrelated.*

*The Sponsor describes that the order of the questions were presented in random order from respondent to respondent to prevent order bias. Because the order in which questions are asked can bias a study, it is important to ask the questions in the same order for each respondent. The order of the questions in the questionnaire submitted, pose potential bias. The first question describes a scenario where Julie who has frequent heartburn mixes the product with two tablespoons of water and drinks it. This is the correct way to use the product and therefore potentially teaches the respondents the correct way prior to answering the remaining questions. Therefore Question 1A should be asked last.*

*Question 4 contains wording that may have biased the respondent. The scenario describes Jen who suffers from frequent heartburn. She loves oatmeal, and opens a Zegerid packet into her morning oatmeal and mixes it thoroughly. The fact that someone "loves oatmeal" may appear to be an unrealistic reason to use it in place of water. An example of a less leading scenario would be "Jen*

is in a hurry, in order to save time she opens a Zegerid packet into her morning oatmeal and mixes it thoroughly.”

Question 6 should have been worded differently if it follow question 5 because it may have set up the respondent to answer question 6 incorrectly. Question 5 describes Julie who has frequent heartburn and decides to use the product. She mixes the product with two tablespoons of water and drinks it. Then the respondent is asked what if anything should she do after she finishes drinking the product. Question 6 asks, “After water is added to the drinking glass and the product is poured into the glass of water, what if anything should be done next?” Because the question starts with “After water is added to the drinking glass” respondents may have been thinking about the answer to question 5 and may not have paid attention to the remainder of the question causing respondents to incorrectly respond “drink it.”

### Data Analysis:

Respondent’s answers were coded as either correct or incorrect. Those who answer incorrectly or vaguely were asked follow-up questions and depending on their response, were coded as acceptable or incorrect.

Correct is defined as a clear understanding of the point of the question.

Acceptable answer is defined as one where the initial understanding is incorrect or ambiguous and the respondent gives the correct answer when probed. These include respondents who changed their minds upon a moment’s reflection and those who simply clarify. A respondent was considered to have successfully met a particular communication objective if he or she presented a correct or acceptable response to the question related to the objective.

An incorrect answer is defined as those where the respondent clearly gives the wrong answer.

Verbatim responses were also provided.

### Summary of Study Results

The primary statistical analysis consisted of point estimates for the proportion of respondents who successfully met each communication objective.

### Demographics

The demographics of the study population are shown in Table 12-15.

**Table 12: Gender**

	Representative Cohort	Low Literacy Cohort
<b>Base: Total per group</b>	<b>400</b>	<b>154</b>
	#	#
	%	%
Male	199 50%	79 51%
Female	201 50%	75 49%

**Table 13: Age**

	Representative Cohort	Low Literacy Cohort
<b>Base: Total per group</b>	<b>400</b>	<b>154</b>
	#	#
	%	%
<b>18 to 34</b>	<b>165</b>	<b>67</b>
	<b>41%</b>	<b>44%</b>
18 – 24	80	40
	20%	26%
25 – 34	85	27
	21%	18%
<b>35 to 54</b>	<b>161</b>	<b>59</b>
	<b>40%</b>	<b>38%</b>
35 – 44	85	25
	21%	16%
45 – 54	76	34
	19%	22%
<b>55+</b>	<b>74</b>	<b>28</b>
	<b>19%</b>	<b>18%</b>
55 – 64	41	18
	10%	12%
65 +	33	10
	8%	7%
Mean	38.96	37.84

**Table 14: REALM Score Distribution**

	Representative Cohort	Low Literacy Cohort
<b>Base: Total</b>	<b>400</b>	<b>154</b>
	#	#
	%	%
1-20	9	13
	2%	8%
21-40	7	20
	2%	13%
41-60	62	121
	16%	79%
61+	322	--
	81%	--
<b>Mean</b>	<b>61.59</b>	<b>48.77</b>

**Table 15: Distribution of Low Literacy and Normal Literacy by Cohort**

	#	%
Representative Cohort	400	
Number of Low Literates in Representative Cohort	78	20%
Number of Normal Literates in Representative Cohort	322	81%
Low Literacy Cohort	154	
Number of Low Literates in Representative Cohort	78	51%
Number of Low Literates in Over-quota	76	50%

## Results

Table 16 and Table 17 show the proportion of correct responses to the questions related to the communication objectives in the Representative cohort and the Low Literacy cohort.

**Table 16: Percent Correct for Questions Related to Communication Objectives- Representative Cohort**

	Representative Cohort
<b>Rep. Base – Representative sample</b>	<b>400</b>
	#
	%
<b>Communication Objectives</b>	
1. Product should be emptied into small cup containing 2 tablespoons of water. <b>Correct</b>	358 90%
2. Product is not to be mixed with any other liquid. <b>Correct</b>	345 86%
3. Product is not to be mixed with any food. <b>Correct</b>	365 91% <sup>a</sup>
4. Product must be stirred well. <b>Correct</b>	364 91% <sup>a</sup>
5 Mixed product must be drunk immediately. <b>Correct</b>	335 84%
6 Another cup of water must be drunk after drinking mixed product. <b>Correct</b>	322 81% <sup>b</sup>

a= significantly statistically higher than upper bound standard of 90% ( $p \leq .05$ ).

b= significantly statistically lower than the upper bound standard of 90% ( $p \leq .05$ ).

**Table 17: Percent Correct for Questions Related to Communication Objectives- Low Literacy Cohort**

	Low Literacy Cohort
<b>Rep. Base – Total Low Literate Frequent Sufferers</b>	<b>154</b>
	#
	%
<b>Primary Communication Objectives</b>	
1. Product should be emptied into small cup containing 2 tablespoons of water. <b>Correct</b>	136 88% <sup>a</sup>
2. Product is not to be mixed with any other liquid. <b>Correct</b>	125 81%
3. Product is not to be mixed with any food. <b>Correct</b>	133 86% <sup>a</sup>
4. Product must be stirred well. <b>Correct</b>	133 86% <sup>a</sup>
5 Mixed product must be drunk immediately. <b>Correct</b>	117 76%
6 Another cup of water must be drunk after drinking mixed product. <b>Correct</b>	125 81%

a= significantly statistically higher than upper bound standard of 85% ( $p \leq .05$ ).

b= significantly statistically lower than upper bound standard of 85% ( $p \leq .05$ ).

Reviewer's Comment

*The range of correct answers to questions related to not mixing the product with food or other liquids is 81-91%. Given that the statement on the label is enhanced in all capital letters (DO NOT USE WITH OTHER LIQUIDS OR FOOD), the range of correct answers should have been much higher. The statement may be confusing in that it states "do not use" versus "do not mix." Respondents may have interpreted "do not use" to mean not to eat or drink when taking the product. The statement should be changed to "do not mix with other liquids or food."*

**Conclusions**

The range of correct responses for the communication objectives in the Representative cohort was 81-90% and 76-81% in the low literacy cohort. As outlined to the Sponsor on February 6, 2008, the design of this study is poor therefore the results from this study can not be used to support consumer comprehension of the labeled directions for Zegerid™ OTC Powder. However, because there are other currently marketed nonprescription drugs formulated as a powder with similar use directions, further testing is not required to support approval.

**Overall Recommendations for Zegerid Nonprescription Labeling Based on Consumer Testing:**

1. Remove sodium bicarbonate and the descriptor (b) (4) from the Principal Display Panel.
2. Under 'Active ingredient' in Drug Facts the purpose of sodium bicarbonate change (b) (4) to "assists in the absorption of omeprazole."
3. Change the statement in the directions for the powder formulation "do not use with other liquids or food" to "do not mix with other liquids or food."

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

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Laura Shay  
9/8/2008 02:34:50 PM  
INTERDISCIPLINARY

Daiva Shetty  
9/8/2008 02:37:37 PM  
MEDICAL OFFICER

**NDA/BLA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

<b>Application Information</b>		
NDA # 22-283 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zegerid OTC Established/Proper Name: Omeprazole and Sodium Bicarbonate Dosage Form: powder for oral suspension Strengths: 20 mg/1680mg		
Applicant: Shering-Plough Agent for Applicant (if applicable): N/A		
Date of Application: 03-19-08 Date of Receipt: 03-20-08 Date clock started after UN: N/A		
PDUFA Goal Date: 01-20-09		Action Goal Date (if different):
Filing Date: 05-19-08 Date of Filing Meeting: 04-28-08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 8		
Proposed Indication(s): Treatment of frequent heartburn		
Type of Original NDA: AND (if applicable)		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal?	<input type="checkbox"/>	
Resubmission after refuse to file?	<input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input checked="" type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division ( <i>if OTC product</i> ): Division of Gastroenterology Products	
List referenced IND Number(s): None listed, however sponsor has IND 74284 for this drug.	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>			
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b> Comprehensive index submitted as an application amendment 05-05-08</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i></b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b><u>PREA</u></b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b>Comments:</b>	
<b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input checked="" type="checkbox"/> <b>Not applicable</b> <input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input type="checkbox"/> <b>Not Applicable</b> <input checked="" type="checkbox"/> Outer carton label <input checked="" type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input checked="" type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): 10-30-07 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 28, 2008

**NDA/BLA #:** NDA 22-283

**PROPRIETARY/ESTABLISHED NAMES:** Zegerid OTC powder for oral suspension/Omeprazole 20mg and sodium bicarbonate 1680 mg

**APPLICANT:** Schering-Plough

**BACKGROUND:** This molecular entity is approved as an Rx medication (NDA 21-636), currently submitted as OTC for different indication and population at the 20mg dosage level. Application is 505(b)(2) using NDA 21-229, Prilosec OTC/omeprazole magnesium, as the OTC listed drug.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Vienna	Y
	CPMS/TL:	Leah Christl	Y
Cross-Discipline Team Leader (CDTL)	N/A		
Clinical	Reviewer:	Christina Chang Wen-Yi Gao (DGP)	Y
	TL:	Daiva Shetty Hugo Gallo-Torres (DGP)	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	Laura Shay	Y
	TL:	N/A	
Labeling Review ( <i>for OTC products</i> )	Reviewer:	Reynold Tan	Y
	TL:	Marina Chang	Y
OSE	Reviewer:	Zachary Oleszczuk	Y
	TL:	Todd Bridges	Y
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	

Clinical Pharmacology	Reviewer:	David Gortler	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	Same as TL	
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	N/A	
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Christopher Hough	Y
	TL:	Shulin Ding	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Other reviewers	N/A		

**OTHER ATTENDEES:** Andrea Leonard-Segal, Director, DNCE; Joel Schiffenbauer, Deputy Director, DNCE; Geri Smith, Regulatory Project Manager, DNCE; Darrell Lyons, Regulatory Project Manager, DNCE; Victor Alexander, Medical Officer, DNCE.

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Application did not contain TESS and DAWN safety data or a comprehensive discussion of the literature related to drug safety.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed? <b>If no</b>, explain: No clinical studies for this NDA</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul>	<input type="checkbox"/> YES

<p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Director, DNCE</p> <p><b>GRMP Timeline Milestones:</b> Filing Date: 05-19-08; Day 74: 06-02-08; Review Completion Goal Date: 11-20-08; PDUFA Goal Date: 01-20-09</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input checked="" type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>

<input type="checkbox"/>	Other
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## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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Mary R Vienna  
8/20/2008 05:08:07 PM  
CSO

## LABELING FILING CHECKLIST FOR A NEW NDA/BLA

<b>NDA Number:</b> NDA 22-281 (Capsules) NDA 22-283 (Powder)	<b>Applicant:</b> Schering-Plough HealthCare Products, Inc. William Cochrane Sr. Manager, Regulatory Affairs (908) 473-1858	<b>Stamp Date:</b> 3/10/08
<b>Drug Name:</b> Zegerid OTC Capsules Zegerid OTC Powder for Oral Suspension	<b>NDA Type:</b> Original submissions	

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary labeling?	X		
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label and package insert labeling, etc)?	X		For capsules: 14-, 28-, 42-ct carton labels Bottle label  For powder: 14-, 2-ct carton labels (b) (4) Powder packet label
3	Does the submission contain the annotated specifications for the "Drug Facts" label?	X		
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?	X		"Zegerid OTC"

Any Additional Comments:

Reynold Tan  
 Reviewing Interdisciplinary Scientist

4/17/08

Date

Supervisor/Team Leader

Date

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

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Reynold Tan  
4/17/2008 01:58:44 PM  
INTERDISCIPLINARY

Marina Chang  
4/17/2008 02:14:46 PM  
INTERDISCIPLINARY