CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-281

OTHER REVIEW(S)

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:	November 5, 2009
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., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label, and Labeling Review
Drug Name:	Zegerid OTC (Omeprazole and Sodium Bicarbonate) Capsules 20 mg/1100 mg
Application Numbers:	NDA 022281
Applicant:	Schering-Plough
OSE RCM #s:	2009-1455

1 BACKGROUND

1.1 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).

1.2 REGULATORY HISTORY

On March 10th, 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. The reference listed drug is Prilosec OTC (NDA 021229). Zegerid OTC is an over-the-counter product used for the treatment of frequent heartburn.

The root name, Zegerid, of the proposed name Zegerid OTC is a proprietary name associated with 4 NDA's. Two of the NDA's (NDA 021636 and 021849) are currently prescription status, one NDA (021850) is not currently marketed and one NDA (021706) has been discontinued.

NDA	Tradename	Ingredients and Strengths	Marketing Status
021636	Zegerid	20 mg omeprazole and 1680 mg sodium bicarbonate powder for suspension and 40 mg omeprazole and 1680 mg sodium bicarbonate powder for oral suspension	Prescription
021849	Zegerid	20 mg omeprazole and 1100 mg sodium bicarbonate capsules and Zegerid 40 mg omeprazole and 1100 mg sodium bicarbonate capsules	Prescription
021850	Zegerid	700 mg magnesium hydroxide, 20 mg omeprazole, and 600 mg sodium bicarbonate chewable tablets and 700 mg magnesium hydroxide, 40 mg omeprazole, and 600 mg sodium bicarbonate chewable tablets	Prescription (not marketed)
021706	Zegerid	40 mg omeprazole and 1680 mg sodium bicarbonate powder for oral suspension	Discontinued

Both prescription products of Zegerid and all strengths (4 total products) that are currently marketed will remain on the market as prescription status when Zegerid OTC is approved. Prescription status Zegerid and Zegerid OTC will share overlapping characteristics such as dosage forms, strengths, dosage, route and frequency, but will not share approved indications. Prescription Zegerid is currently approved for treatment of Duodenal Ulcers, Gastric Ulcers, Symptomatic GERD, Erosive Esophagitis, maintenance of healing of Erosive Esophagitis and Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients while Zegerid OTC will only be approved for frequent heartburn.

2 MATERIAL REVIEWED

Revised container labels, carton and drug facts labeling was submitted on October 23, 2009 (see Appendices A and B). We also evaluated the recommendations pertaining to the label and labeling presented in OSE review #2008-610, dated August 4, 2008, to see if the DMEPA recommendations had been incorporated into the labels and labeling.

3 DISCUSSION

The Division of Medication Error Prevention and Analysis reviewed the revised container labels, carton and drug facts labeling and find the revisions acceptable.

4 CONCLUSIONS AND RECOMMENDATIONS

We have no further comments or recommendations on the container labels, carton and drug facts labeling.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

5 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

/ Other Reviews

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

ZACHARY A OLESZCZUK
11/05/2009

KELLIE A TAYLOR
11/05/2009

DENISE P TOYER
11/05/2009

The following comments are in response to your September 30, 2009 submission of revised labeling for Zegerid™ OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules. These comments are preliminary in nature and should not be considered a complete evaluation of your proposed labeling.

1. Remove the ⌣ that precedes the statement of identity "Sodium Bicarbonate/Allows Absorption of this Omeprazole Product."

( ) b(4)

2. Include the strengths of omeprazole and sodium bicarbonate, 20 mg and 1100 mg, respectively, in the statements of identity, as in previously submitted labels. This information helps consumers compare this product to other omeprazole products.

3. Revise the tamper-evident statement under "Other information" to read, "tamper-evident: do not use if the blue band around the capsule is missing or broken. Do not use if foil inner seal imprinted with "Sealed for your protection" is missing, open or broken." We believe this statement is clearer than the proposed statement.

We request the submission of revised carton and bottle labeling for all package sizes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

MARY RUSSELL R VIENNA
10/16/2009

OTC Drug Labeling Review: Zegerid OTC, Capsules

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

SUBMISSION DATE:	10/22/09	**RECEIVED DATE:**	10/23/09
REVIEW DATE:		11/3/09	
NDA/SUBMISSION TYPE:		NDA 22-281/N-000 Supporting Document 33	
PREVIOUS SUBMISSIONS (Submission Date)		NDA 22-281/N-000, Supporting Document 32 (9/30/09) NDA 22-281/N-000, Supporting Document 30 (7/29/09) NDA 22-281/N-000, response to CR letter (6/6/09) NDA 22-281/N-000, original submission (3/10/08)	
SPONSOR:		Schering-Plough HealthCare Products, Inc. William Cochrane, Sr. Manager, Regulatory Affairs 56 Livingston Ave., Roseland, NJ 07068 862-245-5197	
DRUG PRODUCT(S):		Zegerid OTC, Capsules	
ACTIVE INGREDIENT:		20 mg omeprazole/ 1100 mg sodium bicarbonate	
PHARMACOLOGICAL CATEGORY:		acid reducer/allows absorption of this omeprazole product	
LABELING SUBMITTED:		14-ct bottle label 14-, 28-, and 42-ct carton labels	
REVIEWER:		Reynold Tan	
TEAM LEADER:		Colleen Rogers	

I. Background:

The sponsor's original prescription-to-OTC switch NDA for Zegerid OTC Capsules was submitted on 3/10/08. In a 1/6/09 Complete Response (CR) Letter, we identified issues that prevented us from approving the submission. Several of the issues were labeling issues. The sponsor's 6/6/09 response to the CR Letter included revised labeling to address these issues. In Supporting Document 30, submitted 7/29/09, the sponsor withdrew the ' ' tradename proposed in the 6/6/09 submission. After reviewing the 6/6/09 revised labeling, we sent the sponsor further labeling recommendations on 9/11/09. Supporting Document 32, submitted 9/30/09, included revised labeling that addressed our labeling recommendations on 9/11/09. After reviewing the 9/30/09 revised labeling, we sent the sponsor further labeling recommendations on 10/16/09. Supporting Document 33, submitted 10/22/09, included revised labeling addressing our 10/16/09 recommendations that is being addressed in this label review.

b(4)

In order to record our review of labels submitted prior to 10/22/09 (Supporting Document 33), this label review contains Reviewer's Comments regarding labels submitted on 9/30/09 (Supporting Document 32). Labels submitted prior to 9/30/09 had the same issues that are

addressed in the Reviewer's Comments regarding the 9/30/09 labels. Therefore, Reviewer's Comments regarding Supporting Document 32 (9/30/09 submission) suffice to record our review of labels submitted prior to 10/22/09.

Section II of this label review lists Reviewer's Comments regarding labels submitted in Supporting Document 32 (9/30/09). Section III lists Reviewer's Comments and Reviewer's Recommendations regarding labels submitted in Supporting Document 33 (10/22/09 submission).

II. Labels submitted in NDA 22-281 Supporting Document 32 (9/30/09): Reviewer's Comments requiring changes to labeling were previously communicated to the sponsor. Therefore, a Reviewer's Recommendations section for labels in Supporting Document 32 is not included in this label review.

Reviewer's Comments (Supporting Document 32):

Principal Display Panel and Side Panels

1. Statements of identity for omeprazole and sodium bicarbonate: The sponsor deleted the strengths of omeprazole and sodium bicarbonate, 20 mg and 1100 mg, respectively. The sponsor also added a ' ' before "Sodium Bicarbonate/Allows Absorption of this Omeprazole Product." b(4)

Comment: The sponsor must remove the ' ' that precedes the statement of identity "Sodium Bicarbonate/Allows Absorption of this Omeprazole Product." b(4)

The sponsor should include the strengths of omeprazole and sodium bicarbonate, 20 mg and 1100 mg, respectively, in the statements of identity, as in previously submitted labels. This information helps consumers compare this product to other omeprazole products.

2. Statement of identity for sodium bicarbonate: The sponsor proposes "allows absorption of this omeprazole product."

Comment: This proposed statement of identity for sodium bicarbonate is acceptable. The language is consistent with our recommended language, which read, "permits absorption of this omeprazole product" or "prevents breakdown of this omeprazole product." (Similarly, "allows absorption of this omeprazole product" is acceptable under "Purpose" in Drug Facts to describe the role of sodium bicarbonate in this drug product. See Reviewer's Comments #5 (Supporting Document 32).)

3. [redacted] claim: As recommended, the sponsor removed this claim from the principal display panel. b(4)

Comment: Removing the [redacted] ' claim is acceptable. We requested removal of this claim because [redacted] b(4)

4. [redacted] claim: As recommended, the sponsor removed the term ' [redacted] b(4)
rom the principal display panel and side panels.

[redacted] b(4)

Drug Facts Panel

5. Proposed statement of identity for sodium bicarbonate: The sponsor proposes "allows absorption of this omeprazole product" under "Purpose."

Comment: This proposed statement of identity "allows absorption of this omeprazole product" for sodium bicarbonate under "Purpose" is acceptable. The language is consistent with our recommended language. (See Reviewer's Comments #1 (Supporting Document 32).)

6. "Ask a doctor or pharmacist before use if you are taking" section: As recommended, the sponsor changed " [redacted] to "[bullet] prescription antiretrovirals (medicines for HIV infection)." b(4)

Comment: Changing " [redacted] "[bullet] prescription antiretrovirals (medicines for HIV infection" under "Ask a doctor or pharmacist before use if you are taking" is acceptable. We recommended this change to be consistent with the labeled warning for other approved drug products in this class.

7. "Stop use and ask a doctor if" heading: As recommended, the sponsor revised the subheading "Stop use and ask doctor if" to read, "Stop use and ask a doctor if" (i.e., an "a" was added before "doctor").

Comment: This change is acceptable because "Stop use and ask a doctor if" is the proper subheading.

8. "Directions" statement: As recommended, the sponsor changed "adults 18 years of age and older" to "for adults 18 years of age and older."

Comment: Changing the "Directions" statement "adults 18 years of age and older" to "for adults 18 years of age and older" is acceptable. We recommended the change to clarify that the "Directions" statements that follow the statement pertain to this age group.

9. "Directions" statement: As recommended, the sponsor changed "children under 18 years of age: ask a doctor" to "children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition."

Comment: This change is acceptable. We recommended the change to be consistent with the directions statement for other approved drug products in this class.

10. Tamper-evident statement under "Other information": The statement reads, "tamper-evident: do not use if the blue band around the capsule is missing or broken. Do not use if foil under cap, printed with, "Sealed for your protection" is missing, open or broken."

Comment: This statement should be revised to read, "tamper-evident: do not use if the blue band around the capsule is missing or broken. Do not use if foil inner seal imprinted with "Sealed for your protection" is missing, open or broken." We believe this language is clearer.

III. Labels submitted in NDA 22-281 Supporting Document 33 (10/22/09)

A. Reviewer's Comments (Supporting Document 33): On 10/16/09, we sent the sponsor the following recommendations for revising the labels submitted on 9/30/09:

- Remove the ✓ that precedes the statement of identity "Sodium Bicarbonate/Allows Absorption of this Omeprazole Product." b(4)
- Include the strengths of omeprazole and sodium bicarbonate, 20 mg and 1100 mg, respectively, in the statements of identity, as in previously submitted labels. This information helps consumers compare this product to other omeprazole products.
- Revise the tamper-evident statement under "Other information" to read, "tamper-evident: do not use if the blue band around the capsule is missing or broken. Do not use if foil inner seal imprinted with "Sealed for your protection" is missing, open or broken." We believe this statement is clearer than the proposed statement.

In response, the sponsor submitted labels on 10/22/09 in Supporting Document 33 with the following changes:

1. On the principal display panel, the ——— preceding the statement of identity "Sodium Bicarbonate/Allows Absorption of this Omeprazole Product" was removed. b(4)

Comment: This change was recommended and is acceptable.

2. On the principal display panel, the 20 mg and 1100 mg strengths of omeprazole and sodium bicarbonate, respectively, were added. Bullets preceding the two statements of identity were added.

Comment: Adding the 20 mg and 1100 mg strengths of the active ingredients was recommended and is acceptable. Adding the bullets preceding the two statements of identity is also acceptable. In order to add the 1100 mg strength of sodium bicarbonate, the complete statement of identity for sodium bicarbonate was required to appear over two lines. We informed the sponsor that bullets preceding the statements of identity could be used to help distinguish between the two statements.

3. The tamper-evident statement under "Other information" was revised to read: "tamper-evident: do not use if the blue band around the capsule is missing or broken. Do not use if foil inner seal imprinted with "Sealed for your protection" is missing, open or broken."

Comment: The revised tamper-evident statement uses our recommended language and is acceptable.

B. Reviewer's Recommendation (Supp. Doc. 33): Inform the sponsor that the labels submitted in NDA 22-281 Supporting Document 33 are "Approved." Request final printed labeling, when available, identical to the draft labeling submitted 10/22/09 for all SKUs of the product.

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2 Other Reviews

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

REYNOLD TAN
11/03/2009

COLLEEN K ROGERS
11/03/2009

The following comments are in response to your June 8 and July 29, 2009 submission of revised labeling for Zegerid™ OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules. These comments are preliminary in nature and should not be considered a complete evaluation of your proposed labeling.

1. We continue to recommend "permits absorption of this omeprazole product" or "prevents breakdown of this omeprazole product" as the proposed statement of identity for sodium bicarbonate. We believe consumers will better understand the function of sodium bicarbonate in this product using this language compared to the proposed language (i.e., [redacted]). Also, specifying "this omeprazole product" clarifies that sodium bicarbonate is not necessary to permit the absorption of omeprazole for other omeprazole products. Therefore, the statement of identity for sodium bicarbonate, as it appears on the principal display panels, side panels, and Drug Facts panels, should be revised. b(4)

2. [redacted] b(4)

3 [redacted] b(4)

4. Under "Ask a doctor or pharmacist before use if you are taking", change "[bullet] [redacted] to "[bullet] prescription antiretrovirals (medicines for HIV infection)". This is the new, revised Prilosec warning for the contraindicated use with antiretrovirals. (b)(4)

5. The proposed heading that reads, "Stop use and ask doctor if" must be revised to read, "Stop use and ask a doctor if" (i.e., addition of "a" before "doctor").

6. The "Directions" statement that reads, "adults 18 years of age and older" should be revised to read "for adults 18 years of age and older" to clarify that the "Directions" statements that follow pertain to this age group.

7. The "Directions" statement that reads, "children under 18 years of age: ask a doctor" must be revised to read, "children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition." This revised labeling is consistent with approved Prilosec for proton pump inhibitors.

We request the submission of revised carton and bottle labeling for all package sizes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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/s/

MARY RUSSELL R VIENNA
09/11/2009

Addendum to OTC Drug Labeling Review for Zegerid OTC Capsules

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

SUBMISSION DATE:	April 24, 2008	**RECEIVED DATE:**	April 28, 2008
ADDENDUM DATE:	December 4, 2008		
NDA/SUBMISSION TYPE:	NDA 22-281/N-000 (BL)		
SPONSOR:	Schering-Plough HealthCare Products, Inc. William Cochrane Sr. Manager, Regulatory Affairs (908)473-1858		
DRUG PRODUCT(S):	Zegerid OTC Capsules		
ACTIVE INGREDIENT (PHARMACOLOGICAL CATEGORY):	omeprazole (acid reducer) sodium bicarbonate (assists in the absorption of omeprazole)		
LABELING SUBMITTED:	14-, 28-, 42-ct carton and container (bottle) labels		
REVIEWER:	Reynold Tan		
TEAM LEADER:	Marina Chang		
PROJECT MANAGER	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 revisions 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 "swallow 1 capsule with a glass of water before eating in the morning" to read "swallow 1 capsule with a glass of water 1-hour before eating in the morning." 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] 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"). b(4)

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 "swallow 1 capsule with a glass of water before eating in the morning" to read "swallow 1 capsule with a glass of water 1-hour before eating in the morning." 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.

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3 Other Reviews

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/s/

Reynold Tan
12/4/2008 08:45:03 AM
INTERDISCIPLINARY

Marina Chang
12/4/2008 09:20:48 AM
INTERDISCIPLINARY

OTC Drug Labeling Review for Zegerid OTC Capsules

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

SUBMISSION DATE:	April 24, 2008	**RECEIVED DATE:**	April 28, 2008
REVIEW DATE:		November 20, 2008	
NDA/SUBMISSION TYPE:		NDA 22-281/N-000 (BL)	
SPONSOR:		Schering-Plough HealthCare Products, Inc. William Cochrane Sr. Manager, Regulatory Affairs (908)473-1858	
DRUG PRODUCT(S):		Zegerid OTC Capsules	
ACTIVE INGREDIENT (PHARMACOLOGICAL CATEGORY):		omeprazole (acid reducer) sodium bicarbonate (assists in the absorption of omeprazole)	
LABELING SUBMITTED:		14-, 28-, 42-ct carton and container (bottle) labels	
REVIEWER:		Reynold Tan	
TEAM LEADER:		Marina Chang	
PROJECT MANAGER		Mary Vienna	

Background:

The sponsor submitted draft labels as part of its prescription-to-OTC switch NDA application for Zegerid OTC Capsules. 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 capsule product (NDA 21-849) was approved on February 27, 2006. The approved prescription product contains either 20 mg or 40 mg omeprazole and 1100 mg of sodium bicarbonate.

[redacted] Zegerid OTC Capsule product's multi-panel foldout bottle label. b(4)

Reviewer's Comments:

I. General Comments for Carton and Container Labels

1. The appearance of the tradename "Zegerid OTC$_{TM}$" often shows "OTC$_{TM}$" appearing below "Zegerid." The full tradename "Zegerid OTC$_{TM}$" should appear on the same line, rather than having "OTC$_{TM}$" appear below "Zegerid."

2. The purpose/pharmaceutical category of sodium bicarbonate is listed as ' [redacted] on principal display panels and in the "Active Ingredients" sections of "Drug Facts". This reviewer is recommending the purpose/pharmaceutical category be changed from [redacted] 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. b(4)

II. Carton Labels

A. Principal Display Panels

1. The "NEW" banner must be removed within six months after introduction into the marketplace.

2 [redacted] b(4)

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 "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. *Comment:* The font specifications for the "Drug Facts" label are acceptable.

C. Provision for Lot Number and Expiration Date: Indicate a designated area where the product's lot number and expiration date will appear.

III. Container Labels

A. Multi-panel Foldout Label: The multi-panel foldout container label contains much of the same information as appears on the [redacted] Sections entitled "Who Should Take Zegerid OTC" and "For Questions or Comments About Zegerid OTC" [redacted] do not appear on the Zegerid OTC Capsule product bottle labels. b(4)

[redacted] b(4)

B. "Drug Facts" Labels: See Reviewer's Comments #1 - #4 under "II.B. Carton Labels, 'Drug Facts' Labels."

C. Provision for Lot Number and Expiration Date: Indicate a designated area where the product's lot number and expiration date will appear.

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 Carton and Container Labels

1. Present the full tradename "Zegerid OTC$_{TM}$" on the same line, rather than having "OTC$_{TM}$" appear below "Zegerid."

II. Carton Labels

A. Principal Display Panels

1. Remove the "NEW" banner within six months after introduction into the marketplace.

2. [redacted] b(4)

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.

C. Lot Number and Expiration Date for Carton and Container Labels: Provide an area for lot number and expiration date to appear.

III. "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] to "Assists in the absorption of omeprazole." b(4)

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.

IV. 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

7 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4 Other Reviews

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/s/

Reynold Tan
11/25/2008 12:19:41 PM
INTERDISCIPLINARY

Marina Chang
11/25/2008 01:04:39 PM
INTERDISCIPLINARY

SOCIAL SCIENCE REVIEW

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

NDA: 22-281 b(4)
Type of Submission: New NDA

Product/Ingredient Name:
Zegerid (omeprazole/sodium bicarbonate) OTC™ capsule (NDA 22-281) b(4)

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 b(4)

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 b(4) Labeling implying an b(4) 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 [redacted] but as something such as "to assist in the absorption of omeprazole". b(4)

- 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.

b(4

[redacted] b(4)

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 [redacted] may imply added benefit. [redacted] b(4)

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

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) [redacted] b(4)
Results of [redacted] 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 [redacted]

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 8th 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 [redacted] (n=403)
2. Zegerid™ OTC [redacted] (n=397)
3. Zegerid™ OTC [redacted] (n=407)
4. Prilosec OTC™ (n=409)

b(4)

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

b(4)

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.

CITY:	(12)
Albany ([redacted])	- 1
Appleton ([redacted])	- 2
Atlanta ([redacted])	- 3
Atlanta ([redacted])	- 4
Boston ([redacted])	- 5
Boston ([redacted])	- 6
Boynton Beach ([redacted])	- 7
Charlotte ([redacted])	- 8
Colorado Springs ([redacted])	- 9
Denver ([redacted])	- 0
	(13)
Denver ([redacted])	- 1
Detroit ([redacted])	- 2
Detroit ([redacted])	- 3
Durham ([redacted])	- 4
Eau Claire ([redacted])	- 5
Erie ([redacted])	- 6
Ft. Smith ([redacted])	- 7
Hartford ([redacted])	- 8
Houston ([redacted])	- 9
uston ([redacted])	- 0

CITY:	(14)
Huntington ([redacted])	- 1
Indianapolis ([redacted])	- 2
Jackson ([redacted])	- 3
Kansas City ([redacted])	- 4
Kansas City ([redacted])	- 5
Knoxville ([redacted])	- 6
Los Angeles ([redacted])	- 7
Memphis ([redacted])	- 8
Miami ([redacted])	- 9
Milwaukee ([redacted])	- 0
	(15)
Minneapolis ([redacted])	- 1
Montgomery, AL ([redacted])	- 2
Nashville ([redacted])	- 3
New York ([redacted])	- 4
New York ([redacted])	- 5
Oklahoma City ([redacted])	- 6
Omaha ([redacted])	- 7
Philadelphia ([redacted])	- 8
Phoenix ([redacted])	- 9
Phoenix ([redacted])	- 0

CITY:	(13)
Pittsburgh ([redacted])	- 1
Pittsburgh ([redacted])	- 2
Portland ([redacted])	- 3
Providence ([redacted])	- 4
Puyallup ([redacted])	- 5
Sacramento ([redacted])	- 6
Salt Lake City ([redacted])	- 7
San Diego ([redacted])	- 8
San Diego ([redacted])	- 9
San Francisco ([redacted])	- 0
	(14)
Seattle ([redacted])	- 1
St. Louis ([redacted])	- 2
Tallahassee ([redacted])	- 3
Tampa ([redacted])	- 4
Tulsa ([redacted])	- 5

b(4)

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 (1) [redacted] and the (4) Prilosc 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.

b(4)

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				Prilosec OTC	Total
Representative Sample	403	397	407	409	1616
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%

b(4)

Table 2 Gender Representative Sample/Low Literate Sample

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

b(4)

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

b(4)

Table 3 Age Representative Sample/Low Literate Sample

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

b(4)

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

b(4)

Table 4 Frequency of Heartburn Representative Sample/Low Literate Sample

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

b(4)

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

b(4)

Table 5 REALM Score Representative Sample/Low Literate Sample

b(4)

QJ REALM Test Score	A. Representative Cohort Cells			Prilosec OTC
Rep. Base – total per group	*403*	*397*	*407*	*409*
	# / %	# / %	# / %	# / %
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%
Mean (#)	61.57	60.47	61.73	61.15

b(4)

QJ REALM Test Score	B. Low Literacy Cohort Cells			Prilosec OTC
Low Lit. Base – total per group	*151*	*155*	*153*	*155*
	# / %	# / %	# / %	# / %
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%
Mean (#)	50.34	47.84	51.51	50.32

Table 6 Prilosec OTC Use Representative Sample/Low Literate Sample

b(4)

				Prilosec OTC
Representative	34(8%)	38 (10%)	37 (9%)	35(9%)
Low literate	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^{th}-8^{th} 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 $p \leq .05$.

Table 7 Summary of Primary Communication Objective Findings-Representative Cohort

	A. Representative Cohort			
				Prilosec OTC
Rep. Base – total per group	*403*	*397*	*407*	*409*
	# %	# %	# %	# %
	A	B	C	D
Primary Communication Objectives				
P1. The purpose of sodium bicarbonate – [illegible] ***Correct/Acceptable***	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. ***Correct/Acceptable***	318 79%	301 76%	315 77%	NA
P3. If on a low sodium diet, check with a doctor before use. ***Correct/Acceptable***	374 93%	363 91%	366 90%	NA
P4. It is not to be taken more than once a day. ***Correct/Acceptable***	337 84%	344 87%	366 90%D	342 84%
P5. Product treats frequent heartburn. ***Correct/Acceptable***	370 92%	365 92%	371 91%	376 92%
P6. Product is not for immediate relief. ***Correct/Acceptable***	277 69%	269 68%	307 75%	282 69%
P7. It may take one to four days to take effect. ***Correct/Acceptable***	371 92%	381 96%	383 94%	384 94%
P8. It is to be taken every day for 14 days. ***Correct/Acceptable***	332 82%	346 87%	371 91%D	342 84%

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

b(4)

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

	B. Low Literacy Cohort			
				Prilosec OTC
Low Lit. Base – total per group	*151*	*155*	*153*	*155*
	# %	# %	# %	# %
	A	B	C	D
Primary Communication Objectives				
P1. The purpose of sodium bicarbonate – [illegible] ***Correct/Acceptable***	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. ***Correct/Acceptable***	130 86%	122 79%	131 86%	NA
P3. If on a low sodium diet, check with a doctor before use. ***Correct/Acceptable***	145 96%	144 93%	143 94%	NA
P4. It is not to be taken more than once a day. ***Correct/Acceptable***	129 85%	129 83%	136 89%	128 83%
P5. Product treats frequent heartburn. ***Correct/Acceptable***	138 91%	136 88%	145 95%	139 90%
P6. Product is not for immediate relief. ***Correct/Acceptable***	107 71%	88 57%	108 71%	95 61%
P7. It may take one to four days to take effect. ***Correct/Acceptable***	138 91%	145 94%	141 92%	147 95%
P8. It is to be taken every day for 14 days. ***Correct/Acceptable***	127 84%	131 85%	132 86%	126 81%

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

b(4)

Table 9 Summary of Secondary Communication Objective Findings- Representative Cohort

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

b(4)

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

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

b(4)

Reviewer's Comments

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

[redacted] b(4)

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 303 mg", "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), [redacted] 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 ≥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 ≤ 71% is the question that addresses the statement that describes the product is not for immediate relief. b(4)

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. b(4)

The Sponsor has chosen to use [redacted] 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 This is especially true for the descriptor chosen by the Sponsor ' 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 ' from the (PDP). b(4)
2. Under 'Active ingredient' in Drug Facts the purpose of sodium bicarbonate should be changed from

b(4)

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

6 Other Reviews

b(4)

Overall Recommendations for Zegerid Nonprescription Labeling Based on Consumer Testing:

1. Remove sodium bicarbonate and the descriptor [redacted] from the Principal Display Panel.
2. Under 'Active ingredient' in Drug Facts the purpose of sodium bicarbonate change [redacted] b(4)
3. [redacted]

4 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

5 Other Reviews

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/s/

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

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

LABELING FILING CHECKLIST FOR A NEW NDA/BLA

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

b(4)

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
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"

b(4)

Any Additional Comments:

Reynold Tan — 4/17/08
Reviewing Interdisciplinary Scientist — Date

Supervisor/Team Leader — Date

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/s/

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

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