

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-456**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022456

SUPPL # NA

HFD # 180

Trade Name

Generic Name: Omeprazole, sodium bicarbonate, magnesium hydroxide tablets, 20 mg/750 mg/343 mg and 40 mg/750 mg/343 mg

Applicant Name: Santarus, Inc.

Approval Date, If Known: December 4, 2009

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

*For NDA 22-456, Santarus completed a bridging PK bioequivalence study comparing the 40 mg Chewable Tablets (NDA 21-850) to the 40 mg Tablets (NDA 22-456). Per ONDQA, the 20 mg tablet met the definition of proportionally similar and was granted a bioequivalence/bioavailability waiver based on comparability of dissolution profiles in three media to the 40 mg tablet.*

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

a.

e) Has pediatric exclusivity been granted for this Active Moiety?

*PRILOSEC (omeprazole)* YES  NO

*Sodium bicarbonate* YES  NO

*Magnesium hydroxide* YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

YES  NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	21849	ZEGERID (OMEPRAZOLE, SODIUM BICARBONATE) CAPSULE
(active moiety)	(omeprazole,sodium bicarbonate)	
NDA#	21636	ZEGERID (OMEPRAZOLE, SODIUM BICARBONATE) FOR SUSPENSION
(active moiety)	(omeprazole,sodium bicarbonate)	
NDA#	21850	ZEGERID (OMEPRAZOLE, MAGNESIUM HYDROXIDE, SODIUM BICARBONATE) CHEWABLE TABLET
(active moiety)	(omeprazole,sodium bicarbonate,magnesium hydroxide)	

NDA# 19810 (active moiety)	PRIOSEC (OMEPRAZOLE) CAPSULE, DELAYED RELEASE PELLETS
NDA# 22056 (active moiety)	PRIOSEC (OMEPRAZOLE) FOR SUSPENSION, DELAYED RELEASE
NDA# 21551 (active moiety)	HALFLYTELY (BISACODYL; POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE)
NDA# 20079 (active moiety)	ENDOSOL EXTRA (CALCIUM CHLORIDE; DEXTROSE; GLUTATHIONE DISULFIDE; MAGNESIUM CHLORIDE; POTASSIUMCHLORIDE; SODIUM BICARBONATE;SODIUMCHLORIDE;SODIUMPHOSPHATE)
NDA# 18469 (active moiety)	BSS PLUS (CALCIUM CHLORIDE; DEXTROSE; GLUTATHIONE DISULFIDE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM PHOSPHATE)
NDA# 22193 (active moiety)	NAVSTEL (CALCIUM CHLORIDE; DEXTROSE; GLUTATHIONE DISULFIDE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM PHOSPHATE)
NDA# 21703 (active moiety)	PRISMASOL (CALCIUM CHLORIDE; DEXTROSE; LACTIC ACID; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM BICARBONATE;SODIUM CHLORIDE)
NDA# 20577 (active moiety)	ELLIOTTS B SOLUTION (CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM SULFATE; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE)
NDA# 21910 (active moiety)	NORMOCARB HF 25 (MAGNESIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE)
NDA# 19797 (active moiety)	NULYTELY (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE)
NDA# 90019 (active moiety)	PEG-3350 (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE)
NDA# 76491 (active moiety)	TRILYTE (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE)
NDA# 18983 (active moiety)	COLYTE (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM SULFATE ANHYDROUS)
NDA# 19011 (active moiety)	GOLYTELY (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM SULFATE ANHYDROUS)
NDA# 90231 (active moiety)	PEG 3350 AND ELECTROLYTES (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM SULFATE ANHYDROUS)
NDA# 90186 (active moiety)	PEG 3350 AND ELECTROLYTES (POLYETHYLENE GLYCOL 3350; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM SULFATE ANHYDROUS)
NDA# 77394 (active moiety)	SODIUM BICARBONATE (INJECTABLE)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug



a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
YES  ! NO   
Explain: ! Explain:

Investigation #2 !  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Todd Phillips, PharmD  
Title: Regulatory Project Manager, Division of Gastroenterology Products  
Date: November 23, 2009

Name of Office/Division Director signing form: Donna Griebel, M.D.  
Title: Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22456

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ORIG-1

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SANTARUS INC

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ZEGERID

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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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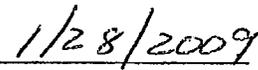
TODD D PHILLIPS  
12/03/2009

DONNA J GRIEBEL  
12/03/2009

### 1.3.3 DEBARMENT CERTIFICATION

Santarus, Inc. 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 new drug application.

  
\_\_\_\_\_  
Maria Bedoya-Toro, Ph.D., M.B.A.  
Vice President, Regulatory Affairs and Quality Assurance

  
\_\_\_\_\_  
Date

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022456 BLA # NA	NDA Supplement # NA BLA STN # NA	If NDA, Efficacy Supplement Type: 3 and 4
Proprietary Name: Established/Proper Name: Omeprazole/Sodium Bicarbonate/Magnesium Hydroxide Dosage Form: Tablet		Applicant: Santarus, Inc. Agent for Applicant (if applicable): NA
RPM: Todd Phillips		Division: Gastroenterology Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p><b>Prilosec® (NDA 019810)</b></p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><b>Application 022456 (omeprazole/sodium bicarbonate/magnesium hydroxide tablet) provides for a change in dosage form from the previously approved NDA 021850 (omeprazole/sodium bicarbonate/magnesium hydroxide chewable tablet). NDA 021850 was approved based upon demonstration of AUC bioequivalence of Zegerid with Magnesium Hydroxide Chewable Tablets, 20 and 40 mg to Prilosec Delayed Release Capsules, 20 and 40 mg (NDA 019810).</b></p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input checked="" type="checkbox"/> No changes      <input type="checkbox"/> Updated Date of check: December 2, 2009</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		December 4, 2009

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____	<input type="checkbox"/> Received

❖ Application Characteristics <sup>2</sup>	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	October 14, 2009
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
• [505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p>	
<p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p>	
<p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	
<p><b>CONTENTS OF ACTION PACKAGE</b></p>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	
<p><b>Officer/Employee List</b></p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<input checked="" type="checkbox"/> Included
<p>Documentation of consent/non-consent by officers/employees</p>	<input checked="" type="checkbox"/> Included
<p><b>Action Letters</b></p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action (approval): December 4, 2009</p>
<p><b>Labeling</b></p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	<p>November 30, 2009</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>January 28, 2009</p>
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>Prilosec DR Capsule and Suspension (RLD), Zegerid Chewable Tablet, Zegerid Capsule and Suspension</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	December 3, 2009
<ul style="list-style-type: none"> <li>❖ Proprietary Name <ul style="list-style-type: none"> <li>• Review(s) (indicate date(s))</li> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> </ul> </li> </ul>	<u>DMEPA</u> Non-acceptability Review: November 17, 2009 Non-acceptability Letter: November 19, 2009 Non-acceptability Letter: May 28, 2009
<ul style="list-style-type: none"> <li>❖ Labeling reviews (indicate dates of reviews and meetings)</li> </ul>	<input checked="" type="checkbox"/> RPM July 20, 2009 <input checked="" type="checkbox"/> DMEPA December 2, 2009; November 6, 2009 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC October 23, 2009 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> SEALD October 28, 2009
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting) (indicate date of each review)</li> </ul>	(b)(2) Assessment: November 24, 2009 RPM Filing Review: April 3, 2009 NonClinical FR: March 24, 2009 Clinical FR: March 27, 2009 ClinPharm FR: April 3, 2009
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (signed by Division Director)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)</li> </ul>	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	December 2, 2009; November 25, 2009; November 16, 2009; November 9, 2009; October 30, 2009; October 26, 2009; October 6, 2009; July 30, 2009; April 3, 2009; February 18, 2009
❖ Internal memoranda, telecons, etc.	August 17, 2009, March 18, 2009
❖ Minutes of Meetings	
• PeRC (indicate date of mtg; approvals only)	<input type="checkbox"/> Not applicable October 14, 2009
• Pre-Approval Safety Conference (indicate date of mtg; approvals only)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (indicate date of mtg)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (indicate date of mtg)	<input type="checkbox"/> No mtg September 9, 2008 (Pre-NDA meeting for IND 075432); April 8, 2008 (tablet formulation discussed at chewable tablet meeting (NDA 021850))
• EOP2 meeting (indicate date of mtg)	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs): DMEPA Proprietary Name	April 30, 2009
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (do not include transcript)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo (indicate date for each review)	<input checked="" type="checkbox"/> None
Division Director Summary Review (indicate date for each review)	<input type="checkbox"/> None December 4, 2009
Cross-Discipline Team Leader Review (indicate date for each review)	<input type="checkbox"/> None December 4, 2009
PMR/PMC Development Templates (indicate total number)	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	November 10, 2009
• Clinical review(s) (indicate date for each review)	October 30, 2009
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input type="checkbox"/> None
❖ Safety update review(s) (indicate location/date if incorporated into another review)	Safety update review included in Medical Officer Review of Safety, October 30, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	October 30, 2009 (page 25 of Clinical Review)

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 8/26/09

❖ Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Document and Supporting Statement (indicate date(s) of submission(s))</li> <li>REMS Memo (indicate date)</li> <li>Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None November 4, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None November 10, 2009, July 8, 2009
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None October 28, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) (indicate date for each review)	<input type="checkbox"/> None December 3, 2009, December 1, 2009, November 18,

	2009
<ul style="list-style-type: none"> <li>• ONDQA Biopharmaceutics review (<i>indicate date for each review</i>)</li> </ul>	August 10, 2009
<ul style="list-style-type: none"> <li>• BLAs only: Facility information review(s) (<i>indicate dates</i>)</li> </ul>	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Microbiology Reviews <ul style="list-style-type: none"> <li>• NDAs: Microbiology reviews (sterility &amp; pyrogenicity) (<i>indicate date of each review</i>)</li> <li>• BLAs: Sterility assurance, product quality microbiology (<i>indicate date of each review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>):</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul> </li> </ul>	November 18, 2009 (page 71 of ONDQA review)
<ul style="list-style-type: none"> <li>❖ Facilities Review/Inspection <ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> <li>• BLAs: <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul> </li> </ul>	Date completed: December 2, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation  Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

### Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

TODD D PHILLIPS  
12/08/2009

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** August 17, 2009  
**TIME:** 1:00 – 2:00 pm EST  
**SPONSOR:** Santarus, Inc.  
**DRUG NAME:** Zegerid® (omeprazole/sodium bicarbonate)  
**TYPE OF MEETING:** Internal Discussion

### FDA ATTENDEES:

Donna Griebel, MD, Director, Division of Gastroenterology Products  
Ruyi He, MD, Acting Deputy Director, Division of Gastroenterology Products  
Erica Wynn, MD, Medical Officer, Division of Gastroenterology Products  
Sushanta Chakder, PhD, Supervisory Pharmacologist, Division of Gastroenterology Products  
Marie Kowblansky, PhD, Supervisor, Office of New Drug Quality Assessment  
Tarun Mehta, PhD, Chemist, Office of New Drug Quality Assessment  
Todd Phillips, PharmD, Regulatory Project Manager, Division of Gastroenterology Products  
Andrea Leonard-Segal, MD, Director, Division of Nonprescription Clinical Evaluation  
Joel Schiffenbauer, MD, Deputy Director, Division of Nonprescription Clinical Evaluation  
Melissa Furness, Supervisory Consumer Safety Officer, Division of Nonprescription Clinical Evaluation  
Daiva Shetty, MD, Medical Officer, Division of Nonprescription Clinical Evaluation  
Mary Vienna, R.N., M.H.A., Regulatory Project Manager, Division of Nonprescription Clinical Evaluation

### MEETING OBJECTIVES:

The purpose of the meeting was to discuss the contents of Zegerid (omeprazole/sodium bicarbonate) and Zegerid with Magnesium Hydroxide and determine how each ingredient should be/is defined (active vs. inactive) and ensure ingredient classification consistency across the Division of Gastroenterology Products (DGP) and the Division of Nonprescription Clinical Evaluation (DNCE).

### DISCUSSION POINTS:

DGP is currently reviewing NDA 22-456 (Zegerid with Magnesium Hydroxide Tablets, 20 and 40 mg).

In 2007, DNCE met with Santarus to discuss Zegerid. During this meeting, DNCE classified sodium bicarbonate as an active ingredient (listed in the active ingredient section of the labeling) which is an adjuvant to assist with the absorption of omeprazole;

no efficacy can be attributed to sodium bicarbonate. Therefore, the Combination Rule does not apply to Zegerid, given the classification of the ingredients.

Historically, DGP classified sodium bicarbonate as an excipient (Zegerid Oral Suspension 20 mg (NDA 21-636) and 40 mg (NDA 21-706)). However, for NDA 21-849 (Zegerid Capsules 20 and 40 mg) DGP changed the classification of sodium bicarbonate from an excipient to an active ingredient. DGP has used the revised classification for all subsequent NDAs (i.e. NDA 21-850, Chewable Tablet). DNCE stated that the sodium bicarbonate classification for the original Zegerid applications (NDA 21-636 and 21-706) has been retrospectively changed from excipient to active ingredient. Per Donna Griebel, DGP will classify sodium bicarbonate as an active ingredient.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

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TODD D PHILLIPS  
12/03/2009

**Phillips, Todd D.**

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**From:** Phillips, Todd D.  
**Sent:** Wednesday, December 02, 2009 6:20 PM  
**To:** Maria Bedoya-Toro, Ph.D  
**Cc:** 'Giles Hulley'; Phillips, Todd D.  
**Subject:** NDA 22-456: container labeling comments, 30NOV09 submission

Dear Maria,

Good evening. Please note the following comments on the container labeling included in the submission dated November 30, 2009. We request response to this request by 03DEC2009.

**Container Labeling:**

Please revise the presentation of the established name to ensure that the words 'Sodium' and 'Bicarbonate' appear on the same line of text. If necessary, you may reduce the size of the font to achieve this revision; however, please ensure that the same font size is used for the entire established name.

Thank you and please let me know if you have any questions.

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

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TODD D PHILLIPS  
12/02/2009

**Phillips, Todd D.**

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**From:** Phillips, Todd D.  
**Sent:** Wednesday, November 25, 2009 3:07 PM  
**To:** Maria Bedoya-Toro, Ph.D  
**Cc:** 'Giles Hulley'; Phillips, Todd D.  
**Subject:** NDA 22-456: PI / container labeling comments, 23NOV09 submission

Dear Maria,

Good afternoon. Please note the following comments on the container and package insert labeling included in the submission dated November 23, 2009. We request responses to our comments by COB Friday (27NOV2009) if possible; if this is not possible, by COB Monday (30NOV2009).

**Container Labeling:**

1. The dosage form should be included as part of the established name. Please revise the established name to appear as stated below:

*OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE TABLETS*

2. Please revise the Healthcare Professional warning on the side panel to appear as stated below:

*"DO NOT substitute OMEPRAZOLE/SODIUM BICARBONATE/MAGNESIUM HYDROXIDE Tablets for ZEGERID Products. Do not substitute two 20 mg OMEPRAZOLE/ SODIUM BICARBONATE/MAGNESIUM HYDROXIDE Tablets for one 40 mg tablet. This will result in taking twice as much sodium bicarbonate and magnesium hydroxide."*

**Package Inset Labeling:**

1. The dosage form should be included as part of the established name. In addition, presenting the established name in all capital letters makes reading the established name more difficult, especially in running text. Please revise the established name of the product to read as follows:

*Omeprazole/Sodium Bicarbonate/Magnesium Hydroxide Tablets*

2. The statement in Section 2.1

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
should be revised to read as follows:

*"Because Omeprazole/Sodium Bicarbonate/Magnesium Hydroxide Tablets contain magnesium hydroxide, the tablets should not be substituted for ZEGERID products (e.g., ZEGERID Powder for Oral Suspension or ZEGERID Capsules)."*

Please let me know if you have any questions. Thank you.

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

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TODD D PHILLIPS  
11/25/2009

**Phillips, Todd D.**

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**From:** Phillips, Todd D.  
**Sent:** Tuesday, November 24, 2009 10:46 AM  
**To:** Phillips, Todd D.  
**Subject:** FW: NDA 22-456 (Zegerid) — B2: cleared for action

b(4)

**From:** Duvall Miller, Beth A  
**Sent:** Monday, November 23, 2009 3:45 PM  
**To:** Phillips, Todd D.  
**Cc:** Quaintance, Kim M; Walsh, Maria R  
**Subject:** NDA 22-456 (Zegerid) — cleared for action

b(4)

Hi Todd,

We discussed your application at today's clearance meeting. You are officially cleared for action from a b(2) perspective.

Have a great day!

Beth

*Beth Duvall-Miller*

Team Leader, Regulatory Affairs Team  
CDER/Office of New Drugs  
Direct Phone Number: (301) 796-0513  
OND IO Phone Number: (301) 796-0700  
Fax: (301) 796-9855

---

**From:** Phillips, Todd D.  
**Sent:** Friday, October 02, 2009 1:22 PM  
**To:** CDER OND IO  
**Cc:** Phillips, Todd D.  
**Subject:** NDA 22-456 (Zegerid) — b2 assessment

b(4)

To Whom It May Concern,

Good afternoon. I have attached the draft (b)(2) assessment for NDA 22-456 (Zegerid) —. The PDUFA goal date for this original NDA is December 4, 2009. Please let me know if you need any additional information.

b(4)

<< File: NDA 22456 b2 assessment\_DRAFT.doc >>

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22456

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ORIG-1

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SANTARUS INC

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ZEGERID

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/s/  
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TODD D PHILLIPS  
11/24/2009

4   Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

**Phillips, Todd D.**

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**From:** Phillips, Todd D.  
**Sent:** Monday, November 16, 2009 9:28 AM  
**To:** Maria Bedoya-Toro, Ph.D  
**Cc:** 'Giles Hulley'; Phillips, Todd D.  
**Subject:** NDA 22-456: revised PI / container comments

**Attachments:** NDA 22-456\_PI\_to sponsor\_16NOV09.doc; NDA 22-456\_PI\_to sponsor\_16NOV09.pdf

Dear Maria,

Good morning. Attached, please find a tracked pdf version of the revised NDA 22-456 package insert along with a clean Word copy.

Please note the following comments on the Zegerid container labeling (included in the submission dated November 12, 2009):

1. Please replace all the instances of 'Zegerid' with the word 'trademark'.

b(4)

We request response to the PI and container comments by COB Wednesday (18NOV2009). If there are any questions, please feel free to contact me. Thank you.



NDA 22-456\_PI\_to  
sponsor\_16NOV...



NDA 22-456\_PI\_to  
sponsor\_16NOV...

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

8 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22456

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ORIG-1

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SANTARUS INC

-----  
ZEGERID

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/s/  
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TODD D PHILLIPS  
11/16/2009

MEMORANDUM

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

DATE: November 10, 2009

TO: Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products (DGP)  
Office of Drug Evaluation III

FROM: Sripal R. Mada, Ph.D. and Sean Y. Kassim, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Mart: K. Yan 11/10/09*  
Associate Director (Bioequivalence)  
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the Review of EIR Covering NDA 22-456  
Zegerid® (Omeprazole / Sodium bicarbonate / Magnesium  
hydroxide) 40 mg tablet from Santarus, Inc.

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

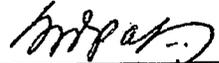
**OME-IR(TAB)-C23:** "A single-dose, randomized, crossover bioequivalence trial of omeprazole administered as Zegerid® with magnesium hydroxide tablets 40 mg and Zegerid® with magnesium hydroxide chewable tablets 40 mg in healthy subjects"

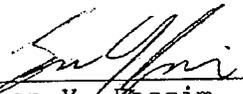
DSI sent an inspection summary memo for the above audit to DGP on July 8, 2009. DSI concluded that the clinical and analytical data from OME-IR(TAB)-C23 are acceptable for review.

This addendum is to inform DGP that DSI received the firm's response (dated July 20, 2009) on July 22, 2009 (Attachment 1). Following our review of the firm's response, DSI's recommendation to DGP in our July 8, 2009 inspection summary memo remains unchanged.

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

Page 2 - NDA 22-456, Zegerid® (Omeprazole / Sodium bicarbonate / Magnesium hydroxide) 40 mg tablet

  
Sripal R. Mada, Ph.D.

  
Sean Y. Kassim, Ph.D.

**Final Classifications:**

**NAI - CEDRA Clinical Research, LLC, San Antonio, Texas**

FEI:

**VAI - \_\_\_\_\_**

FEI: \_\_\_\_\_

b(4)

CC:

DSI/GLPBB/Mada/Kassim/Rivera-Lopez/CF

ODE3/DGP/Griebel/Phillips

OTS/OCP/DCP3/Ahn/Lee

Draft: SRM 11/09/09

Edit: SYK 11/09/09, MKY 11/10/09

DSI: 5947; O:\Bioequiv\EIRCover\22456san.ome.addendum.doc

FACTS: \_\_\_\_\_

b(4)

Email:

CDER DSI PM TRACK

HFR-SW1580/Stone - Patrick.Stone@fda.hhs.gov

4   Page(s) Withheld

  X   Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22456

ORIG-1

SANTARUS INC

ZEGERID

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/s/

-----  
SRIPAL R MADA

11/10/2009

Dr. Yau (acting for Dr. Viswanathan) signed the paper copy on 11/10/2009. Original signed copies are available in the DSI file.

**Phillips, Todd D.**

---

**From:** Phillips, Todd D.  
**Sent:** Monday, November 09, 2009 5:34 PM  
**To:** Maria Bedoya-Toro, Ph.D  
**Cc:** 'Giles Hulley'; Phillips, Todd D.  
**Subject:** NDA 22-456: revised PI / container comments

**Attachments:** NDA 22-456 PI\_to sponsor 09NOV09.pdf; NDA 22-456 PI\_to sponsor 09NOV09.doc

Dear Maria,

Good evening. Attached, please find a tracked pdf version of the revised NDA 22-456 package insert along with a clean Word copy.

In addition to the changes included in the tracked pdf, please note the following comments on the package insert:  
1. Section 17 (Patient Counseling Information): please include a cross-reference for each statement, as appropriate.

b(4)

Please note the following comments on the Zegerid container labeling (included in the 21AUG09 Proprietary Name Review submission):

1. The color scheme of gray for the 20 mg tablets and orange for the 40 mg tablets used for the proposed container labels is similar to the color scheme of the currently marketed product. Using a similar color scheme to differentiate the strengths of each product may introduce vulnerability to confusion that could lead to medication errors involving selection of the wrong drug. In addition to the similar color scheme, the container labels of the proposed product share overlapping numerical strengths (20 mg and 40 mg omeprazole) and two overlapping active ingredients (omeprazole and sodium bicarbonate) with the currently marketed Zegerid container labels. This proposed product and the currently marketed product may be stored in close proximity to one another regardless of the final proprietary name approved for this product. Pharmacies may store medication based on the established name or active ingredients of a product. Since both products contain omeprazole and omeprazole is the first active ingredient stated in both established names, these products may be stored in close proximity to one another. Please revise the color scheme of the container labels for Zegerid to be different than the currently marketed Zegerid product.

b(4)

2. Please include a statement indicating that two 20 mg tablets are not equivalent to one 40 mg tablet (as both the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg)).

We request a response to the PI and container comments by COB Thursday (12NOV2009). If there are any questions, please feel free to contact me. Thank you.



NDA 22-456 PI\_to sponsor 09NOV... NDA 22-456 PI\_to sponsor 09NOV...

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22456

ORIG-1

SANTARUS INC

ZEGERID

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/s/

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TODD D PHILLIPS  
11/10/2009

**Phillips, Todd D.**

---

**From:** Greeley, George  
**Sent:** Thursday, November 05, 2009 9:25 AM  
**To:** Phillips, Todd D.  
**Cc:** Stowe, Ginneh D.  
**Subject:** NDA 22-456 Zegerid

**Importance:** High

Hi Todd,

The Zegerid (omeprazole/sodium bicarbonate/magnesium hydroxide) full waiver was reviewed by the PeRC PREA Subcommittee on October 14, 2009.

The Division recommended a full waivers for each indication because studies would be impossible or highly impracticable and because there are too few children with disease/condition to study.

- 1) short term treatment of active duodenal ulcer
- 2) short term treatment of active benign ulcer
- 3) treatment of heartburn and other symptoms associated with GERD
- 4) short term treatment of erosive esophagitis which has been diagnosed by endoscopy
- 5) Maintenance of Healing of Erosive Esophagitis: maintain healing of erosive esophagitis (controlled studies do not extend beyond 12 months).

Please see the PeRC's recommendations for each waiver:

- 1<sup>st</sup> indication – short tem treatment of active duodenal ulcer (too few children); sponsor's justification no meaningful therapeutic benefit over existing therapies; chewable tablet; uncheck "other" box on pediatric page
- 2<sup>nd</sup> indication – short term treatment (4-8 weeks) of active benign ulcer (too few children); uncheck "other" box on pediatric page
- 3<sup>rd</sup> indication – symptomatic GERD: treatment of heartburn and other symptoms associated with GERD (too few children); uncheck "other" box on pediatric page. The PeRC will has recommended two partial waivers for this indication - too few children for ages 0-1 month and (size of tablet should be removed from peds page) no benefit and efficacy for 1 month to 16 years. Safety information for patients 1 month to 11 months will be transferred from the omeprazole label to the Zegerid label.
- 4<sup>th</sup> indication – Erosive Esophagitis: short term treatment (4 to 8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. There was some data submitted to support extrapolation. The PeRC will has recommended two partial waivers for this indication - too few children for ages 0-1 month and (size of tablet should be removed from pediatric page) no safety and efficacy for 1 month to 16 years.
- 5<sup>th</sup> indication – Maintenance of Healing of Erosive Esophagitis: maintain healing of erosive esophagitis (controlled studies do not extend beyond 12 months). The PeRC has recommended two partial waivers for this indication - too few children for ages 0-1 month and (size of tablet should be removed from pediatric page) no safety and efficacy for 1 month to 16 years.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA/CDER  
10903 New Hampshire Ave.  
Bldg #22, Room 6467  
Silver Spring, MD 20993-0002

301.796.4025

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-22456

ORIG-1

SANTARUS INC

ZEGERID

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/s/

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TODD D PHILLIPS

11/10/2009

**Phillips, Todd D.**

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**From:** Phillips, Todd D.  
**Sent:** Friday, October 30, 2009 4:48 PM  
**To:** Maria Bedoya-Toro, Ph.D  
**Cc:** 'Giles Hulley'; Phillips, Todd D.  
**Subject:** NDA 22-456 revised PI, response requested

**Attachments:** NDA 22456\_TC PI to sponsor 30OCT09.pdf; NDA 22-456 PI to sponsor\_30OCT09.doc

Dear Maria,

Good afternoon. Attached, please find a tracked pdf version of the revised NDA 22-456 package insert along with a clean Word copy.

In addition to the changes included in the tracked PI, please note the following comments:

1. In Section 7 (Drug Interactions), please label the 'Clarithromycin Tissue Concentrations 2 hours after Dose' table as 'Table 3.'
2. The Santarus company logo (located on the final page of the PI) font size is larger than 8 point. Please change the logo font size to 8 point.
3. Please update Section 17 (Patient Counseling Information) to include information for prescribers to convey to patients on how to use the drug safely and effectively (e.g., precautions concerning driving, concomitant use of other substances that may have harmful additive effects, adverse reactions reasonably associated with use of the drug, potential risks and benefits of use of the drug in pregnancy). All broad clinical recommendations should be in the Patient Counseling Information section with a cross reference (as needed) to more detailed information (e.g., Warnings and Precautions, Dosage and Administration) in the PI.

We request a response to the attached version of the PI by COB Friday (06NOV2009). If there are any questions, please feel free to contact me. Thank you.



NDA 22456\_TC PI NDA 22-456 PI to  
to sponsor 30O... sponsor\_30OCT...

Regards,

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
CDER/OND/ODE III  
Food & Drug Administration  
Phone: (301) 796-4857  
Email: Todd.Phillips@fda.hhs.gov

10 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22456

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ORIG-1

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SANTARUS INC

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ZEGERID

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/s/  
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TODD D PHILLIPS  
11/02/2009



NDA 22-456

INFORMATION REQUEST

Santarus, Inc.  
Attention: Maria Bedoya-Toro, PhD, MBA  
Vice President, Regulatory Affairs and QA  
Regulatory Affairs and Quality Assurance  
3721 Valley Center Drive  
Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole/sodium bicarbonate/magnesium hydroxide 20 mg and 40 mg tablets.

We are reviewing the Chemistry, Manufacturing and Control (CMC) section of your submission and have the following comments and information requests. We request your written response as soon as possible in order to continue our evaluation of your NDA:

Please provide the following information regarding the Related Substance of Omeprazole method NPI-OME019 (M-392):

1. As per your validation protocol R080603C for impurities \_\_\_\_\_ the sample solution stability data of the unknown peak at \_\_\_\_\_ do not establish the stability of known impurities \_\_\_\_\_ please provide the sample stability data for the known impurities \_\_\_\_\_
2. As per your validation protocol R080603C for impurities \_\_\_\_\_ the System precision/Method precision (repeatability) data generated using the unknown peak at \_\_\_\_\_ do not qualify this validation parameter. Please perform a System precision/Method precision (repeatability) experiment using the known impurities \_\_\_\_\_

We suggest that you implement the similar validation protocol you have used for the validation of unknown impurities \_\_\_\_\_ or \_\_\_\_\_ **b(4)**

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Todd Phillips, Regulatory Project Manager the Office of New Drugs (Todd.Phillips@fda.hhs.gov).

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

MOO JHONG RHEE  
10/26/2009  
Chief, Branch III



NDA 022456

INFORMATION REQUEST

Santarus, Inc.  
Attention: Maria Bedoya-Toro, PhD, MBA  
Vice President  
Regulatory Affairs and Quality Assurance  
3721 Valley Center Drive Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole/sodium bicarbonate/magnesium hydroxide 20 mg and 40 mg tablets.

We are reviewing the Chemistry, Manufacturing and Control (CMC) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For sodium bicarbonate USP, please provide the retest period with supporting stability data.
2. Please revise the expiration dating period for magnesium hydroxide \_\_\_\_\_ to one year. **b(4)**
3. Please include the tests for \_\_\_\_\_ in your specification which are part of the USP monograph and are included in the manufacturer's release specification. **b(4)**
4. Please include the testing for the \_\_\_\_\_ in the magnesium hydroxide \_\_\_\_\_ specification. **b(4)**
5. You stated (3.2.P.2.3 page 17) that different lots of magnesium hydroxide \_\_\_\_\_ were the root cause for the increased levels of impurity \_\_\_\_\_ in some batches. Please provide explanation as to what variables in the \_\_\_\_\_ affect the formation of impurity \_\_\_\_\_ and how you plan to control these variables. **b(4)**
6. Please revise the drug product specification to account for the amount of \_\_\_\_\_ that is added to the drug product. **b(4)**

7. Please revise the content uniformity testing requirement to include both sodium bicarbonate and magnesium hydroxide content testing.
8. Some of your proposed acceptance criteria in the specification are too liberal, when compared to your clinical and stability batches. Please revise the following:
  - a. The \_\_\_\_\_ range for acid neutralization capacity should be reduced to \_\_\_\_\_ b(4)
  - b. Dissolution acceptance criterion of Q\_\_\_\_\_ at 40 minutes should be revised to Q=\_\_\_\_\_ at 40 minutes.
9. Please submit the validation data for "HPLC method (NPI-OME019) to determine omeprazole related substances in 20 mg and 40 mg tablets" for all known impurities listed in the drug product release specification. Current validation data only qualified the impurity, \_\_\_\_\_ b(4)
10. Please submit the structural identification data for two specified impurities \_\_\_\_\_ and \_\_\_\_\_, which exceed ICH identification thresholds in your product. b(4)
11. Please provide the following information for the container closure system:
  - a. The chemical composition of the \_\_\_\_\_ used in the proposed commercial packaging (HDPE bottles) and/or an exact DMF reference for this information (volume, page, date). b(4)
  - b. The technical purchasing specification of \_\_\_\_\_ used in \_\_\_\_\_ HDPE bottle. b(4)
  - c. A statement that the \_\_\_\_\_ used in the HDPE bottles conforms to CFR requirements for food contact materials.
  - d. Test results from the USP \_\_\_\_\_ and USP <671> (multiple unit containers) tests for the proposed commercial container closures. b(4)
  - e. Dimensional drawings for each packaging component.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment ([Jeannie.David@fda.hhs.gov](mailto:Jeannie.David@fda.hhs.gov)), and Todd Phillips, Regulatory Project Manager the Office of New Drugs ([Todd.Phillips@fda.hhs.gov](mailto:Todd.Phillips@fda.hhs.gov)).

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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/s/

MOO JHONG RHEE  
10/06/2009  
Chief, Branch III



NDA 22-456

**INFORMATION REQUEST LETTER**

Santarus, Inc.  
Attention: Maria Bedoya-Toro, PhD, MBA  
Vice President  
Regulatory Affairs and Quality Assurance  
3721 Valley Center Drive Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole/sodium bicarbonate/magnesium hydroxide 20 and 40 mg tablets.

We also refer to your submission(s) dated January 28, 2009, February 4, 2009, February 27, 2009, March 11, 2009, March 13, 2009, May 27, 2009, June 3, 2009, and June 12, 2009.

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

1. Proposed Package Insert (PI):

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

I. Highlights of Prescribing Information

- a. Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single-spaced, 8 point type with ½ inch margins on all sides, in a two-column format).
- b. Multiple subheadings, under a single heading, must be preceded by a bullet point (i.e. one bullet point for each subheading).
- c. Each summarized statement should be located under the appropriate Highlights heading and must reference the section(s) or subsection(s)

of the Full Prescribing Information (FPI) that contains more detailed information.

- d. For pregnancy category C drugs, pregnancy should be listed under Use in Specific Populations followed by the statement: "Based upon animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." If a pregnancy registry exists, state "Pregnancy registry available." Conclude the entire statement with a cross-reference to Pregnancy section (8.1).
- e. A general customer service email address or a general link to a company website cannot be used to meet the requirements to have adverse reactions reporting contact information in Highlights.

## II. Full Prescribing Information (FPI)

- a. Other than required bolding [CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- b. List adverse reactions (in table format) identified in clinical trials that occurred at or above the specified rate appropriate to the safety database (include: event, number of patients, incidence, and comparators, if appropriate).
- c. For cross-references, do not use all capital letters or bold print. The preferred presentation of cross-references is the section (not subsection) heading followed by the numerical identifier (i.e. [*see Use in Specific Populations (8.4)*]). The cross-reference should be in brackets. Because cross-references are embedded in the text, use of italics to achieve emphasis is encouraged.
- d. The revision date at the end of the Highlights section replaces the revision date at the end of the labeling. The revision date should not appear in both places.
- e. The ~~\_\_\_\_\_~~ statement is not required for package insert labeling and should be deleted. **b(4)**

We request that you submit revised PI labeling by August 31, 2009.

## 2. Clinical Pharmacology

- a. For study OME-IR(TAB)-C23, please recalculate the 90% confidence interval for the mean  $AUC_{(0-t)}$  ratio between Zegerid Tablet 40 mg and Zegerid Chewable

Tablet 40 mg. The results should be summarized in tabular format. Please submit all detailed SAS analysis results along with all PK data in xpt file format.

- b. We request that you submit the final study report and all applicable SAS analyses and datasets for study OME-IR(CAP)-C04.
- c. For study OME-IR(TAB)-C23 and OME-IR(SUSP)-C07, we request that you:
  - i. Provide the definition for adverse event (AE) sequence.
  - ii. Amend the AE tables/datasets to clearly define AE relatedness to treatment, allowing for determination of treatment assignment at the time of AE occurrence.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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CRISTI L STARK  
07/30/2009

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Gastroenterology Products**

**Application Number:** NDA 22-456

**Name of Drug:** omeprazole / sodium bicarbonate / magnesium hydroxide; 20 mg and 40 mg tablets

**Applicant:** Santarus, Inc.

### **Material Reviewed:**

**Submission Date(s):** January 28, 2009 and June 3, 2009

**Receipt Date(s):** February 4, 2009 and June 3, 2009

**Submission Date of Structure Product Labeling (SPL):** June 3, 2009

**Type of Labeling Reviewed:** SPL

### **Background and Summary**

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

### **Review**

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

- I. Highlights of Prescribing Information
  - a. Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single-spaced, 8 point type with ½ inch margins on all sides, in a two-column format).

- b. Multiple subheadings, under a single heading, must be preceded by a bullet point (i.e. one bullet point for each subheading).
- c. Each summarized statement should be located under the appropriate Highlights heading and must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- d. For pregnancy category C drugs, pregnancy should be listed under Use in Specific Populations followed by the statement: “Based upon animal data, may cause fetal harm,” or “No human or animal data. Use only if clearly needed.” If a pregnancy registry exists, state “Pregnancy registry available.” Conclude the entire statement with a cross-reference to Pregnancy section (8.1).
- e. A general customer service email address or a general link to a company website cannot be used to meet the requirements to have adverse reactions reporting contact information in Highlights.

## II. Full Prescribing Information (FPI)

- a. Other than required bolding [CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- b. List adverse reactions (in table format) identified in clinical trials that occurred at or above the specified rate appropriate to the safety database (include: event, number of patients, incidence, and comparators, if appropriate).
- c. For cross-references, do not use all capital letters or bold print. The preferred presentation of cross-references is the section (not subsection) heading followed by the numerical identifier (i.e. [*see Use in Specific Populations (8.4)*]). The cross-reference should be in brackets. Because cross-references are embedded in the text, use of italics to achieve emphasis is encouraged.
- d. The revision date at the end of the Highlights section replaces the revision date at the end of the labeling. The revision date should not appear in both places.
- e. The “~~\_\_\_\_\_~~” statement is not required for package insert labeling and should be deleted.

b(4)

## **Recommendations**

On May 28, 2009, the Division of Medication Error Prevention and Analysis issued a letter to the sponsor rejecting the proprietary name Zegerid® with Magnesium Hydroxide. Upon selection of a revised proprietary name, the sponsor will update the labeling accordingly.

The RPM will request the sponsor address the identified deficiencies/issues and re-submit labeling by August 31, 2009. This updated version of labeling will be used for further labeling discussions.

---

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products

Supervisory Comment/Concurrence:

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Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products

Drafted: TDP / July 2, 2009

Revised/Initialed: CS / July 9, 2009

Finalized: TDP / July 17, 2009

Filename: CSO Labeling Review Template (updated 1-16-07).doc

**CSO LABELING REVIEW OF PLR FORMAT**

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/s/

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Todd Phillips  
7/17/2009 10:50:50 AM  
CSO

Cristi Stark  
7/20/2009 01:16:50 PM  
CSO

MEMORANDUM

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

DATE: July 08, 2009

TO: Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products (DGP)  
Office of Drug Evaluation III

FROM: Sripal R. Mada, Ph.D. and Sean Y. Kassim, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Michael Shelly for CTU 7/8/09*  
Associate Director (Bioequivalence)  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-456 Zegerid® (Omeprazole / Sodium bicarbonate / Magnesium hydroxide) 40 mg tablet from Santarus, Inc.

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

OME-IR(TAB)-C23: "A single-dose, randomized, crossover bioequivalence trial of omeprazole administered as Zegerid® with magnesium hydroxide tablets 40 mg and Zegerid® with magnesium hydroxide chewable tablets 40 mg in healthy subjects"

The clinical portion was conducted at CEDRA Clinical Research LLC in San Antonio, TX, and the analytical portion at \_\_\_\_\_

b(4)

Following inspection of the clinical site (06/17/09 - 06/19/09), FDA Form 483 was not issued.

Following the inspection of the analytical site (June 8 - June 12, 2009), Form FDA-483 was issued (Attachment 1). DSI has not yet received the firm's response to the inspectional findings. The 483 observations for study OME-IR(TAB)-C23 (CEDRA DCN 1002863) and our evaluations follow:

Analytical Site: \_\_\_\_\_

b(4)

1. Failure to perform sufficient Incurred Sample  
Reproducibility assessments. Only 100 of the 5620  
omeprazole samples were reanalyzed. By the current SOP

b(4)

The firm's ISR SOP during the conduct of the study required

The current SOP would require

b(4)

Although not ideal in sample size, the ISR assessment for omeprazole does not indicate a reproducibility concern as 95 out of 100 samples passed the acceptance criterion.

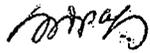
2. Failure to investigate multiple instruments restarts and  
rejection during validation and study sample analysis:

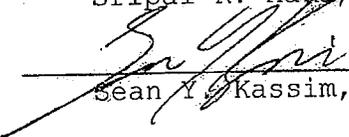
The director of laboratory operations summarized the reinjection / restarts for all the runs. The study director failed to investigate the reasons for repeated instrument failures. Upon review of the chromatograms, however, there were no peak interferences or issues related to peak integrations observed for the accepted runs.

Conclusion:

Following the above inspections, DSI concludes that clinical and analytical data from OME-IR(TAB)-C23 are acceptable for the review.

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

  
Sripal R. Mada, Ph.D.

  
Sean Y. Kassim, Ph.D.

**Final Classifications:**

NAI - CEDRA Clinical Research, LLC, San Antonio, Texas

FEI: \_\_\_\_\_

VAI - \_\_\_\_\_

b(4)

FEI: \_\_\_\_\_

Page 3 - NDA 22-456, Zegerid® (Omeprazole / Sodium bicarbonate / Magnesium hydroxide) 40 mg tablet

cc:

DSI/GLPBB/Mada/Kassim/Rivera-Lopez/CF

ODE3/DGP/Griebel/Phillips

OTS/OCP/DCP3/Ahn/Lee

Draft: SRM 07/01/09

Edit: SYK 07/06/09, JAO 07/07/09

DSI: 5947; O:\Bioequiv\EIRCover\22456san.ome;doc

FACTS: ~~\_\_\_\_\_~~

b(4)

Email:

CDER DSI PM TRACK

HFR-SW1580/Stone - Patrick.Stone@fda.hhs.gov

1   Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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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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Sripal R Mada

7/8/2009 03:50:56 PM

BIOPHARMACEUTICS

Dr. Skelly (Acting for Dr. Viswanathan) signed the paper  
copy on 07/08/2009. Original copies are available on  
request.

3 Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-456

Santarus, Inc.  
Attention: Maria Bedoya-Toro, Ph.D., V.P. RA & QA  
3721 Valley Centre Drive, Suite 400  
San Diego, California 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole/sodium bicarbonate/magnesium hydroxide) 40mg tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 30, 2009. The purpose of the teleconference was to discuss DMEPA's objection to the submitted proposed proprietary name and request a new name submission.

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

If you have any questions, call Nina Ton, Safety Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Denise Toyer, Pharm.D.  
Deputy Director  
Division of Medication Error Prevention  
and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** April 30, 2009  
**TIME:** 1:30 – 2:00 PM EST  
**LOCATION:** Teleconference, WO Bldg 22, RM 5270  
**APPLICATION:** NDA 22-456  
**DRUG NAME:** Omeprazole/sodium bicarbonate/magnesium hydroxide  
**TYPE OF MEETING:** Advice/Clarification

**MEETING CHAIR:** Denise Toyer

**MEETING RECORDER:** Nina Ton

### FDA ATTENDEES:

Office of Surveillance and Epidemiology (OSE)  
Denise Toyer, Deputy Director, DMEPA  
Zachary Oleszczuk, Safety Evaluator, DMEPA  
Cheryl Campbell, Safety Regulatory Project Manger Team Leader  
Nina Ton, Safety Regulatory Project Manager

### Division of Gastroenterology Products (DGP)

Ruyi He, Acting Deputy Division Director  
William Tauber, Medical Officer Team Leader  
Lynne P. Yao, Medical Officer  
Marie Kowblansky, CMC  
Sushanta Chakder, NonClin  
Todd Phillips, Regulatory Project Manger  
Elizabeth Ford, Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES:

Santarus Inc.  
Giles Hulley, Senior Manager RA  
Maria Bedoya-Toro VP RA and QA

### BACKGROUND:

The Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the proposed proprietary name Zegerid for NDA 22-456 and concluded that the name Zegerid is unacceptable. The proposed product contains three active ingredients, Omeprazole, Sodium Bicarbonate, and Magnesium Hydroxide. However, the currently marketed products (NDA 21-636 and NDA 21-849) with the same proprietary name contain only two active ingredients, Omeprazole and Sodium Bicarbonate. In addition, there is another product not currently marketed (NDA 21-850), Zegerid with Magnesium Hydroxide that has the same three active ingredient as the proposed product.

### MEETING OBJECTIVES:

- Discuss the issues identified with the proposed name Zegerid
- Discuss DMEPA's objection to the name Zegerid
- Request a new proprietary name submission

**DISCUSSION POINTS**

- FDA stated that the applicant can not use the same proprietary name, Zegerid, for products with different active ingredients. The proposed drug contains three active ingredients while the marketed products contain only two active ingredients.
- Santarus proposed to add a modifier such as Magnesium Hydroxide to the name Zegerid. FDA informed the applicant that such name would not be acceptable since established names should not be used as part of the proprietary name. FDA also stated that it would object to the name Zegerid with Magnesium Hydroxide since prescribers may abbreviate the modifier to "Mag Ox". In addition, a modifier is often omitted by prescribers when writing prescriptions and patients may get the Omeprazole and Sodium Bicarbonate product instead of the proposed drug. FDA advised the applicant that if they choose to propose a modifier, it must communicate to the prescribers the differences between drug products.
- Santarus inquired about the possibility of the name being acceptable for the proposed product if a commitment was made not to market the chewable tablet (NDA 21-850). FDA noted that it was premature to make any decisions at this time and recommended that the applicant explore different proprietary names and submit a new proposed name.
- FDA inquired if Santarus had considered the secondary name enclosed in the current submission. Santarus stated that they were not sure if they owned the name and would check with their legal department.
- Santarus added that their marketing department had explored the name Zegerid ~~\_\_\_\_\_~~ b(4)  
FDA informed the applicant that such name would not be acceptable since established names should not be used as part of the proprietary name.
- FDA requested clarification on the Package Insert (PI) that included indications of use for both 20 mg and 40 mg tablets, but the submission was only for 40 mg tablets. Santarus stated that they wanted approval for the 40 mg dose. In that case, FDA stated that the applicant would not receive approval for the 20 mg indications.

**DECISIONS (AGREEMENTS) REACHED:**

- Santarus agreed to respond to our comments by the end of June, 2009.

**ACTION ITEMS:**

None

**ATTACHMENTS/HANDOUTS:**

None

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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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Phuong Ton  
5/22/2009 08:04:16 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
5/22/2009 08:16:21 AM  
DRUG SAFETY OFFICE REVIEWER

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

Application Information		
NDA # 22-456	NDA Supplement #:S- NA BLA STN # NA	Efficacy Supplement Type SE- NA
Proprietary Name: Zegerid® Established/Proper Name: omeprazole/sodium bicarbonate/magnesium hydroxide Dosage Form: Tablet Strengths: 40mg/750mg/343mg		
Applicant: Santarus, Inc. Agent for Applicant (if applicable): NA		
Date of Application: January 28, 2009 Date of Receipt: January 29, 2009 Date clock started after UN: February 4, 2009		
PDUFA Goal Date: December 4, 2009		Action Goal Date (if different):
Filing Date: April 5, 2009 Date of Filing Meeting: March 20, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed Indication(s):  1. Short-term treatment of active duodenal ulcer 2. Short-term treatment (4-8 weeks) of active benign gastric ulcer 3. Treatment of heartburn and other symptoms associated with GERD 4. Short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy 5. Maintain healing of erosive esophagitis		
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:  <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 checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <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"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR]	

<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	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 (if OTC product):	
List referenced IND Number(s):  46-656 65-687 69-937 75-432	
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: <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a></i>  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: User fee payment due to FDA on February 3, 2009. Payment was received on February 4, 2009. Applicant was	<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

<p>in arrears; therefore, the new submission receipt date is February 4, 2009.</p>	
<p><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></p>	
<p><b>Exclusivity</b></p>	
<p>Does another product have orphan exclusivity for the same indication? <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> <p>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)]?</p> <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><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</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 <input checked="" type="checkbox"/> NO</p> <p># 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>): The proposed product is a racemic mixture (omeprazole).</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>
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	
<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</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>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"/> 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> <p><b>If yes, please list below:</b>          Three-year exclusivity (pediatric indication) was granted for NDA 22-056. For NDA 22-456, Santarus is requesting indications for adults only. Therefore, in accordance with 314.108 (b)(4)(iv), the exclusivity granted to NDA 22-056 is not infringed upon by NDA 22-456.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 22-056	Omeprazole Magnesium	PED	September 20, 2011
NDA 22-056	Omeprazole Magnesium	NPP	March 20, 2011

*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.*

**Format and Content**

<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 type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input checked="" 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>All portions of the submission are electronic; signature documents are scanned copies.</p>
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<p><b>If electronic submission:</b>          paper forms and certifications signed (non-CTD) or electronic 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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<p><b>If electronic submission, does it follow the eCTD guidance?</b> <i>(<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</i></p> <p><b>If not, explain (e.g., waiver granted):</b> Waiver for use of an electronic hybrid format (electronic NDA in CTD format) was granted by FDA on January 25, 2008. A waiver extension request (waiver through the end of 2009) was granted on September 30, 2008.</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
--	--

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, both 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></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 checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" 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> <p><i>If foreign applicant, both the applicant and the U.S. agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>sign the certification.</i></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 checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input 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>	
<p><b>PREA</b></p> <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><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</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><b>Comments:</b> Initial submission contained a waiver without</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

certification. A corrected application was submitted on 24MAR09.	
<p><b>BPCA (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not applicable <input checked="" 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 checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
<p>Is electronic Content of Labeling submitted in SPL format?</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>Package insert (PI) submitted in PLR format?</p> <p><b>If no, was a waiver or deferral requested before the application was received or in the submission?</b>  <b>If before, what is the status of the request?</b></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  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b> Consult requested on 25MAR09</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b> Santarus did not submit a MedGuide or PPI. Reference drug (Prilosec, NDA 19-810) does not have a MedGuide or PPI.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>REMS consulted to OSE/DRISK?</p> <p><b>Comments:</b> See comments associated with the MedGuide and PPI.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?

- Not Applicable
- YES
- NO

**Comments:** Tradename submission received on March 2, 2009. Confirmation of a complete submission was issued by OSE on March 17, 2009.

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input 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 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 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 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 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> Pre-NDA meeting for NDA 21-850 occurred on April 8, 2008 (Applicant requested submission of a sNDA for new dosage form); Agency required submission of an original NDA. An additional Pre-NDA meeting occurred on September 18, 2008 (IND 75,432).</p>	<input checked="" type="checkbox"/> YES Date(s): April 8, 2008; September 18, 2008 <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>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

<b>Comments:</b>	
------------------	--

ATTACHMENT

MEMO OF FILING MEETING

**DATE:** March 20, 2009

**NDA/BLA #:** 22-456

**PROPRIETARY/ESTABLISHED NAMES:** Zegerid® (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablet, 40mg

**APPLICANT:** Santarus, Inc.

**BACKGROUND:** Santarus currently has three approved forms of Zegerid® (powder for oral suspension (NDA 21-636 and NDA 21-706), capsule (NDA 21-849), and a chewable table with magnesium hydroxide (NDA 21-850)). Santarus originally proposed the development of a new tablet formulation as a supplement to NDA 21-850. The Agency considered the proposed tablet to be a new dosage form, requiring an original NDA. For the original NDA, Santarus proposed a single bioequivalence study comparing the highest strength of Zegerid with Magnesium Hydroxide Tablet to a 40 mg dose of the comparator (Zegerid with Magnesium Hydroxide Chewable Tablet). The Agency agreed with this approach.

The Agency agreed to the inclusion of 3 months of stability data at the time of submission, with 9 months of stability data provided within 90 days of the PDUFA action date.

*(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)*

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Todd Phillips	Y
	CPMS/TL:	Cristi Stark	Y
Cross-Discipline Team Leader (CDTL)	Sue Chih-Lee		N
Clinical	Reviewer:	Lynne Yao	Y
	TL:	William Tauber	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		

	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jane Bai	N
	TL:	Sue-Chih Lee	N
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sushanta Chakder	Y
	TL:		
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Tarun Mehta	N
	TL:	Marie Kowblansky	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

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>List comments: No comments provided during meeting.</p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p>Comments: No review issues identified.</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>Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain: Application contains only bioequivalence data; therefore, a clinical inspection is not required.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> <li>this drug/biologic is not the first in its class</li> <li>the clinical study design was acceptable</li> <li>the application did not raise significant safety or efficacy issues</li> <li>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</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>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p>Comments:</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 <input type="checkbox"/> REFUSE TO FILE

<p><b>Comments:</b> No review issues identified.</p>	<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> Application does not contain any new clinical data.</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> No review issues identified.</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> No review issues identified</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 <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<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
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Division Director</p> <p><b>GRMP Timeline Milestones:</b></p> <ol style="list-style-type: none"> <li>1. Submission Receipt: February 4, 2009</li> <li>2. Day 60 (submission filing date): April 5, 2009</li> <li>3. Day 74 (communicate filing issues): April 19, 2009</li> <li>4. Mid-Cycle Meeting: July 13, 2009</li> <li>5. Communicate Labeling / PMRs to Applicant: October 30, 2009</li> <li>6. Completion Reviews (all): November 11, 2009</li> <li>7. Action Date: December 4, 2009</li> </ol> <p><b>Comments:</b> Timelines were reviewed with preliminary agreement by all relevant team members.</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<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 checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input 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>
<p><b>ACTIONS ITEMS</b></p>	
<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"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## 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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/s/

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Todd Phillips  
4/3/2009 01:47:02 PM  
CSO

Cristi Stark  
4/3/2009 02:34:49 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-456

Santarus, Inc.  
Attention: Maria Bedoya-Toro, PhD, MBA  
Vice President  
Regulatory Affairs and Quality Assurance  
3721 Valley Center Drive Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your new drug application (NDA) dated January 28, 2009, received February 4, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets, 40mg.

We also refer to your submissions dated February 9, 2009, February 27, 2009, March 11, 2009, March 13, 2009 and March 23, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is December 4, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests by October 30, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**REQUIRED PEDIATRIC ASSESSMENTS**

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

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

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Cristi Stark  
4/3/2009 01:13:57 PM

## PDUFA Clock Restart

(This form must be completed upon applicant removal from the arrears list.)

**Applicant:** Santarus, Inc.

**Date Firm Removed From Arrears List (Payment Date):** February 4, 2009

NDA #	Supplement (S) or Reviewable Unit (RU) #
22-456	Original application

**PROJECT MANAGER:** Todd Phillips

HFD-180

### NOTES:

1. The user fee clock restarts on the date the firm was removed from arrears list. This date is from the daily "User Fee Payment & Arrears List" e-mail.
2. In DFS, link the form only to the initial submission of the NDA (original N document) or the supplement (base document) or the Reviewable Unit (RU).
3. This form performs different functions depending on how it is checked into DFS.
  - a. If checked in as:  
Document type: "FORMS"  
Form group: "ADMINISTRATIVE"  
Form name: "PDUFA Clock Restart"  
then it informs the DDR to create an AR document, which restarts the clock as of the payment date.
  - b. If checked in as:  
Document type: "FORMS"  
Form group: "ADMINISTRATIVE"  
Form name: "Establishment UN & PDUFA Clock Restart"  
then it informs the DDR to stop the clock with an UN decision as of the submission receipt date and also create an AR document, which restarts the clock as of the payment date.
  - c. If checked in as:  
Document type: "FORMS"  
Form group: "ADMINISTRATIVE"  
Form name: "Application UN & PDUFA Clock Restart"  
then it informs the DDR to stop the clock with an UN decision as of the submission receipt date plus 5 calendar days and also create an AR document, which restarts the clock as of the payment date.
4. The document room will create a document with amendment type "AR" for each listed application/supplement/reviewable unit on the form. The payment date will be used as the letter date, stamp date, and decision date. After this document has been created, prepare an "Acknowledge Receipt of Owed User Fee" letter and link it to the "AR" document in DFS.

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/s/

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Todd Phillips  
3/18/2009 01:51:33 PM

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

<b>Application Information</b>		
NDA # 022456	NDA Supplement #: S- NA	Efficacy Supplement Type SE- NA
Proprietary Name: Zegerid® Established/Proper Name: omeprazole/sodium bicarbonate/magnesium hydroxide Dosage Form: Tablet Strengths: 20 and 40 mg omeprazole/750 mg sodium bicarbonate/343 mg magnesium hydroxide Applicant: Santarus, Inc.		
Date of Receipt: January 29, 2009 (User Fee Payment Received: February 4, 2009)		
PDUFA Goal Date: December 4, 2009		Action Goal Date (if different):
Proposed Indication(s): 1. Short-term treatment of active duodenal ulcer 2. Short-term treatment (4-8 weeks) of active benign gastric ulcer 3. Treatment of heartburn and other symptoms associated with GERD 4. Short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy 5. Maintain healing of erosive esophagitis		

b(4)

<b>GENERAL INFORMATION</b>
----------------------------

- 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)
<b>Prilosec® (AstraZeneca / (NDA 19-810)</b>	<b>Santarus referenced Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg</b>

\*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)

**Zegerid® Suspension (NDA 21-636), Capsule (NDA 21-849) and Chewable Tablet (NDA 21-850) applications were supported by pharmacokinetic and pharmacodynamic studies that compared the PK and PD profiles of each Zegerid® formulation with Prilosec® Delayed Release Capsules at steady state.**

**For NDA 22-456, Santarus completed a bridging PK bioequivalence study comparing the 40 mg Chewable Tablets (NDA 21-850) to the 40 mg Tablets (NDA 22-456). Per ONDQA, the 20 mg tablet met the definition of proportionally similar and was granted a bioequivalence/bioavailability waiver based on comparability of dissolution profiles in three media to the 40 mg tablet.**

**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)
<b>Prilosec® (AstraZeneca)</b>	<b>19-810</b>	<b>Yes (Form 356h)</b>

*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").

**Application 22-456 (tablet) provides for a change in dosage form from the previously approved NDA 21-850 (chewable tablet).**

*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 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):

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 21-850, Zegerid® with Magnesium Hydroxide Chewable Tablet**

<b>PATENT CERTIFICATION/STATEMENTS</b>
--

- 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):

6147103  
6147103\*PED  
  
6150380  
6150380\*PED  
  
6166213  
6166213\*PED  
  
6191148  
6191148\*PED

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)



6191148

6191148\*PED

- (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):

**40 mg Tablet**

AstraZeneca LP: April 8, 2009

AstraZeneca AB: April 8, 2009

Merck & Co. (Whitehouse Station): April 8, 2009

Merck & Co. (Rahway): April 8, 2009

**20 mg Tablet**

AstraZeneca LP: June 5, 2009

AstraZeneca AB: June 8, 2009

Merck & Co. (Whitehouse Station): June 8, 2009

Merck & Co. (Rahway): June 5, 2009

- (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



DEPARTMENT OF HEALTH & HUMAN  
SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-456

Santarus, Inc.

Attention: Maria Bedoya-Toro, PhD, MBA  
Vice President  
Regulatory Affairs and Quality Assurance  
3721 Valley Center Drive Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

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

Name of Drug Product:	Zegerid® with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets 40mg / 750mg / 343mg
Date of Application:	January 28, 2009
Receipt Date of User Fees:	February 4, 2009
Our Reference Number:	NDA 22-456

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received on February 4, 2009, all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 5, 2009, in accordance with 21 CFR 314.101(a).

NDA 22-456

Page 2

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Todd Phillips, Regulatory Project Manager, at (301) 796-4857.

Sincerely,

*{See appended electronic signature page}*

Todd Phillips, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

-----  
**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/

-----  
Todd Phillips  
2/18/2009 07:57:03 AM

**From:** Strongin, Brian K  
**Sent:** Tuesday, September 09, 2008 4:53 PM  
**To:** 'MBedoya-Toro@santarus.com'  
**Cc:** Strongin, Brian K  
**Subject:** Preliminary Responses for September 18 Pre-NDA Meeting for IND 75,432  
Maria,

Here are our preliminary responses to the questions included in the background package for the September 18, 2008 pre-NDA meeting. Thanks.

Pre-NDA Meeting: IND 75,432 Zegerid with Magnesium Hydroxide Tablets  
September 18, 2008 10AM  
Conference Room 1315  
Preliminary Responses

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 18, 2008 between Santarus Inc. and the Division of Gastroenterology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact me to discuss the possibility of including these for discussion at the meeting.

Please note that you will be responsible for summarizing key discussion points, agreements, clarifications, and action items as appropriate.

Pre-NDA Meeting: IND 75,432 Zegerid with Magnesium Hydroxide Tablets  
September 18, 2008 10AM  
Conference Room 1315

Chemistry, Manufacturing, and Controls

1. ...

Santarus believes it has demonstrated that the Zegerid family of products has shown consistent and similar stability trends between dosage formulations. Since the Zegerid tablet developmental material also shows similar trends, does the Agency agree that a reduced stability data set of 3 months data at time of submission will support the Fileability of the application?

**Response: Your proposal to provide only three months of stability data at the time of submission for each product strength and all packaging configurations, and to supplement the application with 9 months of stability data no later than 90 days prior to the PDUFA date is acceptable.**

2. The sponsor proposes to submit the drug product specifications listed in Table 5 below for Zegerid with Magnesium Hydroxide Tablets. Santarus believes that the proposed specifications are appropriate to ensure the Quality of Zegerid tablets. Does the Agency agree?

**Response: Based on the limited information that you have provided in your briefing package, the proposed product attributes that you intend to include in the specification are acceptable, but the test methods and numerical values of the acceptance criteria will be evaluated in the context of your entire NDA submission. You will need to submit entire dissolution profiles for your products so that we may determine the acceptability of your proposed dissolution acceptance criteria.**

Regulatory

3. ... Does the agency agree that these documents will support the approval of the tablet NDA?

**Response: While these appear to be the correct types of information to submit in your NDA, a decision regarding the adequacy and approvability of the application requires a complete review of your application.**

**From:** Maria Bedoya-Toro, Ph.D., MBA [mailto:MBedoya-Toro@santarus.com]  
**Sent:** Thursday, July 17, 2008 3:22 PM  
**To:** Strongin, Brian K

**Subject:** FW: Zegerid with Magnesium Hydroxide Tables IND 75,432 -Type B (pre-NDA) Meeting Request  
**Importance:** High

Brian: Per our discussion today, attached, please find the Type B (pre-NDA) Meeting Request for Zegerid with Magnesium Hydroxide Tables IND 75,432. If you have any questions, please call me at the telephone number below. Kind regards Maria

*Maria Bedoya-Toro*

V.P. RA & QA

Santarus, Inc.

(858) 314-5715 | Direct

(858) 314-5704 | FAX

[mbedoya-toro@santarus.com](mailto:mbedoya-toro@santarus.com)

Linked Applications

Sponsor Name

Drug Name

IND 75432

SANTARUS INC

SAN-20 (MAGNESIUM  
HYDROXIDE/OMEPRazole/S

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

/s/

BRIAN K STRONGIN

09/09/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-850

Santarus Inc.  
Attention: Maria Bedoya-Toro, Ph.D., M.B.A.  
3721 Valley Centre Drive, Suite 400  
San Diego, CA 92130

Dear Dr. Bedoya-Toro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 8, 2008. The purpose of the meeting was to discuss plans to introduce a swallowable tablet dosage form of Zegerid immediate-release omeprazole.

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

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

*{See appended electronic signature page}*

Elizabeth A.S. Ford, R.N.  
Regulatory Health Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B Meeting  
**Meeting Category:** Pre NDA meeting  
**Meeting Date and Time:** April 8, 2008; 9:00 AM  
**Meeting Location:** White Oak Building 22, Room 1309  
**Application Number:** NDA 21-850  
**Product Name:** Zegerid with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets  
**Received Briefing Package** March 7, 2008  
**Sponsor Name:** Santarus, Inc.  
**Meeting Requestor:** Amanda M. Omlor, MS RAC; Manager, Regulatory Affairs  
**Meeting Chair:** Hugo Gallo-Torres, M.D., Ph.D., P.N.S.  
**Meeting Recorder:** Elizabeth A.S. Ford, R.N.

**Meeting Attendees:**

**FDA Attendees**

Donna Griebel, M.D., Director, Division of Gastroenterology Products

Joyce Korvick, M.D., M.S., Deputy Director, Division of Gastroenterology Products

Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Medical Team Leader, Division of Gastroenterology Products

Wen-Yi Gao, M.D., Medical Officer, Division of Gastroenterology Products

Jane Bai, Ph.D. Clinical Pharmacology and Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics II

David Lewis, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment

Charles Wu, Ph.D., Pharmacologist, Division of Gastroenterology Products

Sushanta Chakder, Ph.D., Pharmacologist, Division of Gastroenterology Products

Brian Strongin, R.Ph., M.B.A., Chief, Project Management Staff, Division of Gastroenterology Products

Elizabeth A.S. Ford, R.N., Regulatory Health Project Manager, Division of Gastroenterology Products

**Sponsor Attendees**

Maria Bedoya-Toro, Ph.D., M.B.A., Vice President, Regulatory Affairs and Quality Assurance

Warren Hall, Senior Vice President, Manufacturing and Product Development

E. David Ballard, M.D., Vice President, Clinical Research and Medical Affairs

Craig Bowe, Manger, Stability and Analytical Development

## 1.0 BACKGROUND

This Type B Meeting was requested by Santarus, Inc. in correspondence to the FDA, dated January 18, 2008, received January 23, 2008, to discuss plans to introduce a swallowable tablet dosage form of Zegerid immediate-release omeprazole.

Santarus has reformulated Zegerid with Magnesium Hydroxide Chewable Tablets (NDA 21-850), which has not been commercially marketed, to provide for a swallowable tablet. The sponsor intends to submit a prior approval supplement to NDA 21-850 to provide for Zegerid with Magnesium Hydroxide (omeprazole/sodium bicarbonate/magnesium hydroxide) Tablets; and would like to review, at the meeting, the requirements for submission and approval of a supplemental NDA for the new swallowable tablet formulation.

## 2.0 DISCUSSION

### Question 1 – Stability

The sponsor proposes to include stability data from one lot of each strength (20 mg/750 mg/350 mg and 40 mg/750 mg/350 mg) of Zegerid with Magnesium Hydroxide Tablets stored at accelerated conditions (40°C/75% RH) for 3 months in the SNDA and the sponsor commits to the submission of long-term stability data from these two lots in the NDA annual reports. Does the Agency agree that this will be sufficient to support an expiration dating for the swallowable tablets that \_\_\_\_\_ months?

### Response:

**No. From a CMC perspective, we do not feel that this proposed dosage form is a new formulation of the current Zegerid® Chewable Tablet. We recommend the evaluation of the proposed tablet as a new dosage form. In order to petition for its approval by the agency, an NDA should be submitted. Reference is made to the regulations and guidances. Please see “Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees” as well as guidances for format and content of an NDA including 21 CFR §314.50 and the CTDQ.**

Stability data submitted to support an application for a new drug product should, in general, be consistent with ICH Q1A(R2), Stability Testing of New Drug Substances and Products. It should include data from at least three primary batches from each of the two strengths (data from at least six batches total) of the proposed drug product, packaged in the container closure(s) intended for market, stored at long-term, accelerated, and (if appropriate) intermediate conditions.

We do not agree that this situation is the same as that which existed with NDA 21-849 / SCF-002 for Zegerid® Capsules, which was approved in December 2007. In that situation, only one component of the 20 & 40 mg formulations (magnesium stearate) which functioned as \_\_\_\_\_, was replaced by another substance (sodium stearyl fumarate) **b(4)**

which served the same function. \_\_\_\_\_

b(4)

By contrast, the proposed swallowable tablet possesses a completely different formulation, different size and weight, a different particle size of omeprazole, and one component that was not part of the formulation of the Chewable Tablet (sodium stearyl fumarate).

\_\_\_\_\_. It is noted that changes in the amount of drug substance are not addressed by the Guidance for Industry: Immediate Release Solid Oral Dosage Forms, Scale-Up and post-Approval Changes (November 1995), which was referenced on pg. 4 of the pre-meeting package.

b(4)

Finally, in the CDER Data Standards Manual C-DRG-00201 (for Dosage Form), Tablet (no. 500) and Chewable Tablet (no. 501) are regarded as different dosage forms.

Additional Discussion:

*Santarus, Inc. presented information about the formulation changes in the drug substance as related to excipients and active ingredients, and acknowledged the differences between the chewable tablet and the swallowable tablet. Santarus expressed they would like to demonstrate equivalence between the two products in order: \_\_\_\_\_ obtained with the chewable tablet; this was identified as motivation for requesting permission to submit the swallowable tablet as a prior approval supplement. Santarus acknowledged that "tablet" and "tablet, chewable" are listed as different formulations in The Orange Book, however they would still like to pursue this application as a supplement rather than as a new NDA.*

b(4)

*The FDA acknowledged that the quantity of the drug substance has not changed, and that the potency is the same between the formulations. However, the proposed change is considered to be a new dosage form, requiring a new NDA. Reference was made to the Orange Book, appendix C, and to CDER Data Standards Manual C-DRG-00201.*

*Santarus, Inc. will submit a proposal to NDA 21-850 for review by Mike Jones, Special Assistant, Office of Regulatory Policy, CDER, requesting consideration for submission of the swallowable tablet as a supplemental NDA.*

*Santarus would like to submit 3 months of accelerated stability data at the time of submission, and augment the data with a total of 3 lots to be updated during the review cycle at 6 and 9 months.*

*The FDA noted that 3 months of accelerated stability data available for review at the time of submission would be considered a reduced data set. Therefore, the Agency cannot comment on the acceptability of this plan without seeing the data. We recommend submitting 3 batches of stability data. The assigned expiry will be defined by the data reviewed at the end of the review cycle. If the plan is to update these data at 6 months and 9 months, we cannot guarantee that the NDA would be fileable. We recommend you submit a proposal to your NDA for review by the appropriate division prior to the submission of the new NDA. Please refer to ICH Q1A(R2), Stability Testing of New Drug Substances and Products for the recommended stability dataset for NDA submission (Section II.B.7), and to ICH Q1C, Stability*

*Testing for New Dosage Forms, in which the acceptability of a reduced stability dataset at submission time is addressed (this Guidance is an annex consisting of only 1 page of text).*

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### **Question 2 – Dissolution**

The dissolution data generated to date suggest that the swallowable tablet dissolves faster than the whole chewable tablet. Because the dissolution test for the chewable tablet is conducted on a large intact tablet with no accommodation for simulated chewing, this result was not unexpected. To address the differences between the chewable tablet and the swallowable tablet, the sponsor commits to developing and validating a dissolution method for the swallowable tablet and establishing new specifications, in order to provide appropriate quality control of the finished drug product. Does the Agency agree that a validated and specific dissolution method and the establishment of new dissolution specifications will be an acceptable approach to provide appropriate quality control of the dissolution profile of the finished drug product?

#### **Response:**

**The development of a separate analytical procedure and acceptance criteria for the proposed swallowable tablet (separate with respect to that which is used for the Chewable Tablet) is not objectionable. However, release and stability data for the proposed (swallowable) tablet should not be collected until the proposed dissolution method is developed and validated. Dissolution data for the proposed tablet using the analytical procedure developed for the current (chewable) tablet should be used only as supportive data.**

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### **Question 3 – Biopharmaceutics**

The sponsor proposes to conduct a pharmacokinetic bioequivalence study in healthy adult volunteers. The study will be a single-dose, randomized, crossover, two-period design with an appropriate sample size. Each volunteer will receive Zegerid with Magnesium Hydroxide Tablets 40 mg and an omeprazole comparator product in random order; blood samples will be collected prior to dosing and at frequent post-dose time points for assessment of pharmacokinetic parameters. We believe that it is reasonable to include only the 40 mg strength in the bioequivalence study to support the approval of the 20 mg and 40 mg Zegerid with Magnesium Hydroxide Tablets because the dose-response relationship for omeprazole has consistently been shown to be linear. Does the Agency agree that a finding of bioequivalence utilizing the highest dose strength (40 mg) of the Zegerid with Magnesium Hydroxide Tablets compared to a 40 mg dose of the comparator will be acceptable for approval of both the 20 mg and 40 mg Zegerid with Magnesium Hydroxide Tablet products?

#### **Response:**

**Using the highest strength of Zegerid with Magnesium Hydroxide Tablets to compare with a 40 mg dose of the comparator is acceptable, based on the formulations for both strengths provided by the sponsor.**

**Additional Discussion:**

*Santarus Inc. proposed using the chewable tablet as a comparator if they decide to pursue the submission of the swallowable tablet as a new NDA rather than as a prior approval supplement.*

*The Agency referred to the above response given in question 3.*

---

**Question 4 – Biopharmaceutics**

Does the Agency agree that either 40 mg Zegerid with Magnesium Hydroxide Chewable Tablets or 40 mg Prilosec capsules can be used as the study comparator?

**Response:**

**If no clinical study will be conducted for the swallowable tablet, we recommend that you use the 40 mg Zegerid with Magnesium Hydroxide Chewable Tablets as the reference product since it has the same additional active ingredients.**

---

**Question 5 – Regulatory**

Santarus proposes to submit the following documentation in support of the prior approval supplement to NDA 21-850:

- a) A pharmacokinetic bioequivalence study comparing the 40 mg strength of Zegerid with Magnesium Hydroxide Tablets and an omeprazole appropriate comparator product. We believe this is sufficient to provide for regulatory approval of both the 20 mg and 40 mg strengths because of the dose linearity that has been consistently demonstrated for omeprazole in the Zegerid products.

b)

b(4)

- c) Full information regarding the CMC information required for the manufacture, control, and testing of the tablets at the Norwich Pharmaceuticals facility.

d)

b(4)

e)

b(4)

Does the Agency agree that these documents will support the approval of the Zegerid with Magnesium Hydroxide Tablets SNDA?

**Response:**

**No. See responses to the Questions above. A complete NDA should be submitted to request approval to market the proposed Zegerid with magnesium hydroxide tablet.**

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**4.0 ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Santarus Inc. will submit a detailed proposal to NDA 21-850 asking Mike Jones to consider whether the application for approval for the swallowable tablet may be reviewed by the division as a prior approval supplement rather than as a new NDA.	Sponsor/ FDA will forward the submission to Mike Jones for review upon arrival.	N/A
Santarus, Inc. will submit a detailed proposal outlining the reviewable stability data at the time of the submission and timing for updates of the stability data during the review cycle.	Sponsor/FDA will route to the appropriate review team for a decision.	N/A

**5.0 ATTACHMENTS AND HANDOUTS**

None

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this page is the manifestation of the electronic signature.**  
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/s/

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Elizabeth A Ford  
5/7/2008 04:01:50 PM