

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-706

Administrative/Correspondence Reviews

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-706	Efficacy Supplement Type N/A	Supplement Number N/A	
Drug: Omeprazole Powder for Oral Suspension, 40mg		Applicant: Santarus, Inc.	
RPM: Mary M. Lewis		HFD-180	Phone # 301-827-7475
Application Type: ☐ 505(b)(1) ☒ <u>505(b)(2)</u>		Reference Listed Drug (NDA #, Drug name): NDA 19-810 Prilosec® (omeprazole) Capsules	
❖ Application Classifications:			
- Review priority - Chem class (NDAs only) - Other (e.g., orphan, OTC)		☒ Standard ☐ Priority 3 N/A	
❖ User Fee Goal Dates		December 26, 2004	
❖ Special programs (indicate all that apply)		☒ None Subpart H ☐ 21 CFR 314.510 (accelerated approval) ☐ 21 CFR 314.520 (restricted distribution) ☐ Fast Track ☐ Rolling Review	
❖ User Fee Information			
- User Fee - User Fee waiver		☒ Paid ☐ Small business ☐ Public health ☐ Barrier-to-Innovation ☐ Other ☐ Orphan designation ☐ No-fee 505(b)(2) ☐ Other	
❖ User Fee exception			
❖ Application Integrity Policy (AIP)			
- Applicant is on the AIP - This application is on the AIP - Exception for review (Center Director's memo) - OC clearance for approval		☐ Yes ☒ No ☐ Yes ☒ No	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		☒ Verified ☐ N/A	
❖ Patent			
- Information: Verify that patent information was submitted - Patent certification [505(b)(2) applications]: Verify type of certifications submitted		☒ Verified 21 CFR 314.50(i)(1)(i)(A) ☐ I ☒ II ☐ III ☒ IV 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii) ☒ Verified ☐ N/A	
For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).			
❖ Exclusivity Summary (approvals only)		(In Draft)	

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	5/27/04
Actions	
• Proposed action	(X?) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable () None () Press Release () Talk Paper () Dear Health Care Professional Letter
• Indicate what types (if any) of information dissemination are anticipated	
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	X (11/22/04)
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	X
Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
Outgoing correspondence (i.e., letters, E-mails, faxes)	
Memoranda and Telecons	
Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
❖ Clinical review(s) (indicate date for each review)	11/12/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	11/12/04 Clinical Review p.10
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	11/19/04
❖ Biopharmaceutical review(s) (indicate date for each review)	10/28/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/23/04
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	11/1/04; 10/15/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	11/1/04
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report) (tentative: 11/23/04 Withhold)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation Per CMC Review: not required. (Page 5 of 8, 11/2/04 Review)	() Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	12/13/02; 09/29/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

SANTARUS, INC.
CONFIDENTIAL

NDA 21-706
1.3.1. Patent Information
Page 1

1.3.1 PATENT INFORMATION

The following patent information is submitted in accordance with 21 CFR §314.53:

US Patent No.	Expiration Date	Type	Patent Owner
5,840,737	July 16, 2016	Method of Use	The Curators of the University of Missouri
6,489,346	July 16, 2016	Composition; Method of Use	The Curators of the University of Missouri
6,645,988	July 16, 2016	Composition; Method of Use	The Curators of the University of Missouri

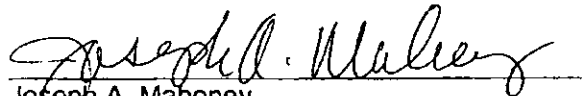
The undersigned declares that the above stated United States Patent Numbers 5,840,737, 6,489,346, and 6,645,988 cover the composition and/or method of use of OSB-IR, which product is the subject of this application for which approval is being sought.

Signature:

Name:

Title:

Date:



Joseph A. Mahoney

Patent Counsel

February 17, 2004

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-706	
		NAME OF APPLICANT / NDA HOLDER	
		Santarus, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME)			
TBD			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
Omeprazole		40 mg	
DOSAGE FORM			
Immediate-Release Powder for Oral Suspension			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	
6,489,346		December 3, 2002	
		c. Expiration Date of Patent	
		July 16, 2016	
d. Name of Patent Owner		Address (of Patent Owner)	
The Curators of the University of Missouri		615 Locust Street	
		City/State	
		Columbia, MO	
		ZIP Code	
65211		FAX Number (if available)	
		(573) 882-1160	
Telephone Number		E-Mail Address (if available)	
(573) 884-3903		SharpeT@missouri.edu	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
			
		City/State	
		ZIP Code	
		FAX Number (if available)	
		E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
☐ Yes ☒ No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
☐ Yes ☐ No			

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

2. Drug Substance (Active Ingredient)

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

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

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

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

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

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

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

3. Drug Product (Composition/Formulation)

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

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

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

4. Method of Use

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

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

4.2 Patent Claim Number (as listed in the patent) Claims 91 - 94 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Proposed labeling: for short-term treatment (4 - 8 weeks) of active benign gastric ulcer; and for the of upper gastrointestinal bleeding in critically ill patients.

5. No Relevant Patents

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

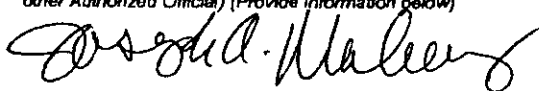
6. Declaration Certification

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

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

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

Date Signed



2/17/04

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

Check applicable box and provide information below.

☐ NDA Applicant/Holder

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

☐ Patent Owner

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

Name

Joseph A. Mahoney, Mayer, Brown, Rowe & Maw LLP

Address

190 S. LaSalle Street

City/State

Chicago

ZIP Code

IL

Telephone Number

312-701-8979

FAX Number (if available)

312-706-9000

E-Mail Address (if available)

Jamahoney@mayerbrownrowe.com

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

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 <i>See OMB Statement on Page 3.</i>	
		21-706	
		NAME OF APPLICANT / NDA HOLDER Santarus, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) TBD			
ACTIVE INGREDIENT(S) Omeprazole		STRENGTH(S) 40 mg	
DOSAGE FORM Immediate-Release Powder for Oral Suspension			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 5,840,737		b. Issue Date of Patent November 24, 1998	
		c. Expiration Date of Patent July 16, 2016	
d. Name of Patent Owner The Curators of the University of Missouri		Address (of Patent Owner) 615 Locust Street	
		City/State Columbia, MO	
		ZIP Code 65211	FAX Number (if available) (573) 882-1160
		Telephone Number (573) 884-3903	E-Mail Address (if available) SharpeT@missouri.edu
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) 		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No			

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

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No
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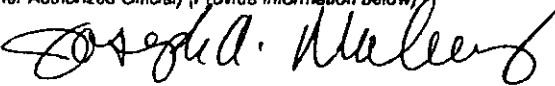
- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 4.2 Patent Claim Number (as listed in the patent)
Claims 1, 2 and 4 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Proposed labeling: for short-term treatment (4 – 8 weeks) of active benign gastric ulcer; and for the — of upper gastrointestinal bleeding in critically ill patients.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) 	Date Signed 2/17/04
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Check applicable box and provide information below.	
☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Joseph A. Mahoney, Mayer, Brown, Rowe & Maw, LLP	
Address 190 S. LaSalle St.	City/State Chicago
ZIP Code 60603	Telephone Number 312-701-8979
FAX Number (if available) 312-706-9000	E-Mail Address (if available) Jamahoney@mayerbrownrowe.com
The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857 <i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number</i>	

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
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a. United States Patent Number		b. Issue Date of Patent	
6,645,988		November 11, 2003	
		c. Expiration Date of Patent	
		July 16, 2016	
d. Name of Patent Owner		Address (of Patent Owner)	
The Curators of the University of Missouri		615 Locust Street	
		City/State	
		Columbia, MO	
		ZIP Code	
		FAX Number (if available)	
		(573) 882-1160	
		E-Mail Address (if available)	
		SharpeT@missouri.edu	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in f.e.)	
		City/State	
		ZIP Code	
		FAX Number (if available)	
		E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
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- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

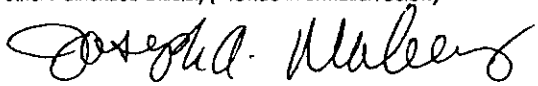
4. Method of Use

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

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

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

8. Declaration Certification	
8.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct. Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below) 	Date Signed 2/17/04
NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).	
Check applicable box and provide information below.	
☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Joseph A. Mahoney, Mayer, Brown, Rowe & Maw LLP	
Address 190 S. LaSalle St.	City/State Chicago
ZIP Code 60603	Telephone Number 312-701-8979
FAX Number (if available) 312-706-9000	E-Mail Address (if available) Jamahoney@mayerbrownrowe.com
The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857 <i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i>	

1.3.2 PATENT CERTIFICATIONS

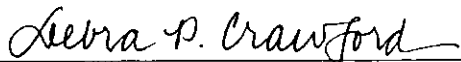
Paragraph II Certification

Pursuant to §505(b)(2)(A)(ii) of the Federal Food, Drug and Cosmetic Act and the Food and Drug Administration regulations 21 CFR §314.50(i)(1)(i)(A)(2), Santarus, Inc. hereby certifies with respect to United States Patent Number 4,508,905, that the patent has expired.

Paragraph IV Certification

Pursuant to §505(b)(2)(A)(iv) of the Federal Food, Drug and Cosmetic Act and Food and Drug Administration regulation 21 CFR §314.50(i)(1)(i)(A)(4), Santarus, Inc. hereby certifies with respect to each of United States Patent Numbers 4,786,505, 4,853,230, 6,147,103, 6,150,380, 6,166,213, and 6,191,148 that such patent is invalid or will not be infringed by the manufacture, use, or sale of OSB-IR, for which this §505(b)(2) application is submitted.

Pursuant to 21 CFR §314.50(i)(1)(i)(A)(4), Santarus, Inc. certifies that the owners of United States Patent Numbers 4,786,505, 4,853,230, 6,147,103, 6,150,380, 6,166,213, and 6,191,148 and the holder of the approved New Drug Application #19-810, will be sent notification of non-infringement and/or invalidity of the above-referenced patents as required by 21 CFR §314.52(a) that contains the information described in 21 CFR §314.52(c).



Debra P. Crawford
Senior Vice President and Chief Financial Officer

EXCLUSIVITY SUMMARY FOR NDA # 21-706

SUPPL # N/A

Trade Name: ZEGERID

Generic Name: Omeprazole Powder for
Oral Suspension, 40 mg

Applicant Name: Santarus, Inc

HFD # 180

Approval Date If Known: 12/ /2004

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / 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 / X / 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES / ☒ / NO / ___ /

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

three years.

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

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

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 / **X** / NO /___/

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

NDA# 19-810 Prilosec Capsules

NDA# 21-153 Nexium

NDA# _____

2. Combination product. N/A

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# _____

NDA# _____

NDA# _____

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 NDA'S 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 / X / 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 /X / 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 /X/ 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 /X/

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 /X/

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:

OSB - IRC03

OSB - IRC02

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 product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /X/ NO /___/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Prilosec NDA 19-810 _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /X/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Prilosec NDA 19-810 _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

OSB - IRC03 [] of upper gastrointestinal bleeding
in critically ill patients.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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 #46,656 YES /X/ ! 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 /___/ Explain _____ ! NO /___/ Explain _____
!
!

!

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ 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 /X/

If yes, explain: _____

Signature: Mary M. Lewis Date: 12/___/2004
Title: Regulatory Project Manager

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

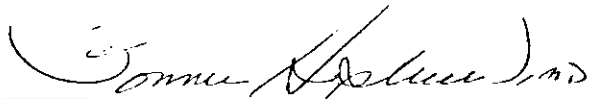
1.3.9 Statement of Claimed Exclusivity and Associated Certifications

Santarus, Inc. is claiming three years of marketing exclusivity for the indication of ☐ of upper gastrointestinal bleeding in critically ill patients under the provisions of 21 CFR §314.108. This claim is being made because the information included in this NDA meets the criteria described in 21 CFR §314.108(4)(i-iv). 1

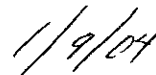
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1.3.3 Debarment Certification

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.



Bonnie Hepburn, MD
Chief Medical Officer, Vice President Drug Development



Date



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 12/21/04

To: Christine Simmons	From: Mary Lewis
Company: Santarus, Inc.	
Fax number: 858-314-5701	Fax number: 301-443-9285
Phone number: 858-314-5700	Phone number: 301-827-7475
Subject: Approval Letter NOA 21-706	

Total no. of pages including cover: 22

Comments: Attached are the Approval Letter and agreed upon labeling signed off on today.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

127 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

 _____ § 552(b)(5) Draft Labeling

12/8/04

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-706

Supplement # N/A

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **ZEGERID Powder for Oral Suspension**

Generic Name: **Omeprazole**

Strengths: **40mg**

Applicant: **Santarus, Inc.**

Date of Application: **February 25, 2004**

Date of Receipt: **February 26, 2004**

Date clock started after UN: **N/A**

Date of Filing Meeting: **March 26, 2004**

Filing Date: **April 26, 2004**

Action Goal Date (optional): **December 15, 2004**

User Fee Goal Date: **12/26/04**

Indication(s) requested: Short-term treatment (4-8) weeks of active benign gastric ulcer; and, — of upper GI bleeding in critically-ill patients.

Type of Original NDA: (b)(1) _____ **(b)(2) X**
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

____ NDA is a (b)(1) application OR ____ NDA is a (b)(2) application

Therapeutic Classification: **S X**

P _____

Resubmission after withdrawal? **N/A**

Resubmission after refuse to file? _____

Chemical Classification: (1,2,3 etc.) **3**

Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted:

XYES

NO

User Fee Status:

Paid X Exempt (orphan, government) _____

Waived (e.g., small business, public health) _____

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES XNO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES XNO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES XNO
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? XYES NO
- Was form 356h included with an authorized signature? XYES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? XYES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A XYES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A XYES NO
- Is it an electronic CTD? N/A YES XNO
If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Clinical, statistical, Quality Module 3, Module 5 clinical study reports, labeling, summary volume, pharmtox, administrative information.

Additional comments:

- Patent information submitted on form FDA 3542a? **XYES** NO
- Exclusivity requested? **YES: 3years** NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **X YES** NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&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 . . ."

- Financial Disclosure forms included with authorized signature? **XYES** NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? **XYES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **XYES** NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: **IND 46,656**
- End-of-Phase 2 Meeting(s)? **Date(s) _____ XNO**
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? **Date(s) 6/10/03** NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **XYES** NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **XYES** NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? XN/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? XN/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? XN/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? XN/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? XYES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
 NO
- Establishment Evaluation Request (EER) submitted to DMPQ? XYES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? XN/A YES NO

Appears This Way
On Original

ATTACHMENT
MEMO OF FILING MEETING

Refer to Administrative Review dated 5/27/04, in DFS.

DATE:

BACKGROUND:

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

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	
Secondary Medical:	
Statistical:	
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE _____ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ XNO
- 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? N/A YES NO

CLINICAL MICROBIOLOGY NA _____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS	FILE _____	REFUSE TO FILE _____
• Biopharm. inspection needed:		YES NO
PHARMACOLOGY	NA _____ FILE _____	REFUSE TO FILE _____
• GLP inspection needed:		YES NO
CHEMISTRY	FILE _____	REFUSE TO FILE _____
• Establishment(s) ready for inspection?		YES NO
• Microbiology		YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

- _____ The application is unsuitable for filing. Explain why:
- _____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
- _____ No filing issues have been identified.
- _____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? **XYES** NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

Prilosec NDA 19-810

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES **XNO**

(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))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? **XYES** NO

(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.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? **XYES** NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in 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 capsules to solution").

New dosage form: powder; 40mg strength; ☒ of upper gastrointestinal bleeding in critically ill patients.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES **XNO**
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? YES **XNO**

(See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)).

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES XNO
10. Are there certifications for each of the patents listed for the listed drug(s)? XYES NO
11. 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.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

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

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

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

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

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

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
Clinical and Pharmtox **XYES** NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
XYES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A **XYES** NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
N/A YES **XNO**

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
XYES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
XYES NO
- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.
IND # 46,656 NO
OR
A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?
YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

XYES

NO

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/s/

Mary Lewis
12/8/04 09:20:32 AM
CSO

Lewis, Mary

From: Lewis, Mary
Sent: Friday, December 03, 2004 10:55 AM
To: Charles Davis (cdavis@santarus.com)
Cc: Christine M. Simmons
Subject: NDA21706 Email Labeling & DDMAC.doc

Please see the attached email. If you have any question, please call me. Mary

MEMORANDUM OF TELECON

DATE of email: December 3, 2004

APPLICATION No.: NDA 21-706

BETWEEN:

Name: Charles Davis
Senior Director, Regulatory Affairs
Phone: 858-314-5753
Representing: Santarus, Inc.

AND

Name: Mary M. Lewis
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products, HFD 180

SUBJECT: NDA 21-706, Zegerid, 40mg, packet and carton label

Original Message from Charles Davis:

From: Charley Davis [CDavis@santarus.com]
Sent: Wednesday, December 01, 2004 3:31 PM
To: Lewis, Mary
Subject: RE: NDA 21-706, Zegerid 40mg, packet label

Hi Mary,

We are very confused by this response. We were under the impression that the Division agreed that this phrase was appropriate to add to the Directions for Use on the packet label and box label for Zegerid 40 mg. If we delete this simple phrase there will be a mismatch between the Directions for Use on the packet and box labels and the package insert. Zegerid Powder for Oral Suspension 40 mg will be indicated for "Reduction of Risk of Upper Gastrointestinal Bleeding in Critically-Ill Patients." For such patients nasogastric or orogastric tube administration of omeprazole is commonplace and the Dosage and Administration section of the Zegerid 40 mg package insert provides the appropriate information. If we delete the phrase about nasogastric/orogastric tube administration the packet and box labels will include directions referring only to mixing and drinking Zegerid. There was no disagreement or

12/3/2004

question about the nasogastric/orogastric paragraph in the Dosage and Administration section of package insert during our November 18, 2004 conference call. In that conference call we agreed that inclusion of the phrase "See package insert for nasogastric/orogastric tube administration" was appropriate for the packet and box labels.

Moreover, the comment about the insertion, "See package insert for nasogastric/orogastric tube administration" requiring fair balance (appropriate risk information) is troubling. This sentence is no different in meaning or purpose and makes no more representation about the product than do the companion directions, "Mix packet contents with 1-2 tablespoons of WATER in a small cup. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink."

We would appreciate it very much if this issue could be reconsidered by the review team.

If there are questions please do not hesitate to call.

Regards,
Charley Davis

FDA Response:

Upon further review with DDMAC, we have decided that you can include the statement "See package insert for nasogastric/orogastric tube administration" on the packet label and the carton without the need for fair balance.

Mary M. Lewis
Regulatory Project Manager

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

/s/

Mary Lewis
12/3/04 10:41:39 AM
CSO

Lewis, Mary

From: Benedetto, Shannon
Sent: Friday, December 03, 2004 10:02 AM
To: Lewis, Mary
Cc: Strongin, Brian K; Abrams, Thomas W; Hu, Elaine
Subject: RE: NDA 21-706, Zegerid 40mg, packet label

Mary,

Based on further review, DDMAC has decided that the sponsor can include the statement "See package insert for nasogastric/orogastric tube administration" without the need for fair balance.

Regards,

Shannon

-----Original Message-----

From: Lewis, Mary
Sent: Thursday, December 02, 2004 1:50 PM
To: Benedetto, Shannon
Cc: Strongin, Brian K
Subject: FW: NDA 21-706, Zegerid 40mg, packet label
Importance: High

Hi Shannon,

Please see the email below from Santarus.

With regard to inserting the phrase about the 'nasogastric and orogastric tube' it was my understanding from our 11/18/04 telecon with the Company that this was in relation to the package insert, and not in relation to the packet label or the carton.

After reading this attached email, let me know your response. Thank you.

FYI: The PDUFA date on this is 12/26/04.

Mary

-----Original Message-----

From: Charley Davis [mailto:CDavis@santarus.com]
Sent: Wednesday, December 01, 2004 3:31 PM
To: Lewis, Mary
Subject: RE: NDA 21-706, Zegerid 40mg, packet label

Hi Mary,

We are very confused by this response. We were under the impression that the Division agreed that this phrase was appropriate to add to the Directions for Use on the packet label and box label for Zegerid 40 mg. If we delete this simple phrase there will be a mismatch between the Directions for Use on the packet and box labels and the package insert. Zegerid Powder for Oral Suspension 40 mg will be indicated for "Reduction of Risk of Upper Gastrointestinal Bleeding in Critically-Ill Patients." For such patients nasogastric or orogastric tube administration of omeprazole is commonplace and the Dosage and Administration section of the Zegerid 40 mg package insert provides

12/3/2004

the appropriate information. If we delete the phrase about nasogastric/orogastric tube administration the packet and box labels will include directions referring only to mixing and drinking Zegerid. There was no disagreement or question about the nasogastric/orogastric paragraph in the Dosage and Administration section of package insert during our November 18, 2004 conference call. In that conference call we agreed that inclusion of the phrase "See package insert for nasogastric/orogastric tube administration" was appropriate for the packet and box labels.

Moreover, the comment about the insertion, "See package insert for nasogastric/orogastric tube administration" requiring fair balance (appropriate risk information) is troubling. This sentence is no different in meaning or purpose and makes no more representation about the product than do the companion directions, "Mix packet contents with 1-2 tablespoons of WATER in a small cup. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink."

We would appreciate it very much if this issue could be reconsidered by the review team.

If there are questions please do not hesitate to call.

Regards,

Charley Davis

From: Lewis, Mary [mailto:LewisMA@cder.fda.gov]

Sent: Tuesday, November 30, 2004 1:29 PM

To: Charley Davis

Subject: NDA 21-706, Zegerid 40mg, packet label

<<09001464804b1bd3.pdf>>

Hi Charley,

Here is our response to your email of November 18, 2004.

If you have any questions, please call.

Thank you.

Mary

301-827-7475

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 12/1/2004

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Acting Division Director Approval Comments
NDA 21-706

APPLICANT: Santarus, INC.

DRUG: Zegerid® (Omeprazole powder for oral suspension), 40 mg

DIVISION RECOMMENDATION:

The Division recommends approval of the proposed indication reworded as follows:

“ZEGERID™ is indicated for the reduction of risk of upper gastrointestinal bleeding in critically ill patients.”

“ZEGERID™ Powder for Oral Suspension is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer.”

I am in agreement.

I. Regulatory History:

Previously, NDA 21-636 was approved for Zegerid (20 mg omeprazole powder) for oral suspension, for short-term (4-8 weeks) active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis. Zegerid 20mg was approved 6/15/04.

This application is a 505(b)(2) based upon the active moiety omeprazole. This is an immediate release product, which relies upon the buffering action of bicarbonate to protect the omeprazole from degradation in the stomach. Currently marketed products are delayed-release formulations of marketed omeprazole.

This NDA (21-706) provides omeprazole powder for oral suspension at the 40 mg dose. The proposed indications are for short-term treatment of active benign gastric ulcers and — of upper GI bleeding in critically ill patients. The first indication, is an approved indication for the reference drug, omeprazole delayed-release.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

No substantial issues were noted in these reviews, comments on wording for the package insert were made in labeling discussions. The name was found to be acceptable.

B. Chemistry and Manufacturing:

The chemistry review team found this application acceptable, and did not recommend any post approval commitments.

C. Pre-Clinical Pharmacology/Toxicology:

This was a 505(b)(2) submission relying on the FDA findings of safety and efficacy of omeprazole. Thus, the sponsor did not provide any new animal pharmacology/toxicology information. The application was found acceptable by the reviewers. Labeling comments were made (see final label attached to approval letter).

D. Biopharmaceutics:

From the viewpoint of OCPB, this NDA is acceptable provided the label wording could be agreed upon. This formulation of Zegerid is the same as the already approved 20-mg product; the only difference is the amount of omeprazole in the formulation (40 mg).

According to the reviewer "Data was submitted from two clinical pharmacology studies (OSB-IR-C05 and OSB-IR-C02) investigating the pharmacokinetics and pharmacodynamics of OSB-IR 40 mg. Study OSB-IR-C02 evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of omeprazole following administration of multiple 40 mg doses of OSB-IR and Prilosec Delayed Release Capsule. As expected, OSB-IR 40 mg was not bioequivalent to Prilosec delayed release capsules 40 mg. Although, AUC was similar, C_{max} was higher for OSB-IR 40 mg (by 51.1 % on day 1 and 19.5% on day 7). Despite the differences in pharmacokinetics, OSB-IR and Prilosec Capsule were generally similar with respect to the pharmacodynamics of intragastric pH. Significant food-effect was observed for OSB-IR with C_{max} and AUC decreasing by 60% and 27%, respectively following administration of 40 mg OSB-IR 1 hour post-meal relative to administration 1 hour pre-meal. Study OSB-IR-C05 is an open label study that evaluated the safety and pharmacokinetics (PK) of two consecutive 40 mg doses of OSB-IR administered within 6 hours of each other. C_{max} and AUC of omeprazole increased by 30% and 100%, respectively, following administration of a second 40 mg dose of OSB-IR within 6 hours of a 40 mg dose of OSB-IR, which is consistent with the

increase in omeprazole systemic exposure observed following administration of OSB-IR 40 mg for 7 days.”

E. Clinical/Statistical:

The applicant requested an indication, which is currently in the omeprazole label for the 40 mg dose, treatment of benign gastric ulcer. This is acceptable because Zegerid was demonstrated to be equivalent for the AUC and were in an acceptable range for the C_{max}. C_{max} was somewhat greater with this formulation than the delayed release formulation. In addition to the supportive pharmacokinetics, the pharmacodynamics indicated that the acid suppressing activity was preserved. Therefore, these data along with clinical safety data of omeprazole powder allow us to rely on our previous finding of omeprazole (delayed release) efficacy for short-term treatment (4-8 weeks) of active benign gastric ulcer.

The remainder of this section will consider the second proposed indication: short-term treatment of active benign gastric ulcers and — of upper GI bleeding in critically ill patients.

Efficacy:

The efficacy of this therapeutic approach, the — of upper GI bleeding in critically ill patients, was based upon one well-controlled clinical trial. This study demonstrated non-inferiority to the only approved therapy for this indication; continuous infusion of intravenous cimetidine.

The primary results were as follows: 10 patients in the cimetidine group (10/181, 5.5%) and 7 patients in the Zegerid group (7/178, 3.9%) were found to have clinically significant GI bleeding. The primary efficacy endpoint of this trial was the occurrence of clinically significant UGI bleeding defined as: bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or persistent Gastrocult®-positive coffee-ground material for at least eight consecutive hours in Day 1 and 2 (three consecutive gastric aspirates within 2 to 4 hours for Day 3 and 4) that did not clear with at least 100 mL of lavage with room temperature normal saline. This study along with the pharmacokinetic data was sufficiently convincing regarding the primary outcome to recommend approval of this oral indication. Omeprazole is a powerful inhibitor of gastric acid, and this route of administration appears to be effective based upon efficacy data and pharmacokinetic data in the critically ill patients. In addition, Zegerid may provide caregivers with an alternate route of administration, which may be of benefit in this situation.

Safety

No new safety concerns were raised by this NDA.

III. Labeling Recommendations:

In general, the label was harmonized with the approved 20 mg dose label, and the new indications for the 40 mg dose were added. In addition, concern was expressed by the Division regarding the amount and type of pharmacodynamic data, which was placed in the label under the clinical trial section. The compromise agreement was to use a standard cut off of pH 4 to describe the effect of this formulation on gastric acid. In addition the timing of the measurement was an important consideration, in that during the first hour in the early days of the study the degree of change in pH for some patients may have been more reflective of the active excipient than the activity of omeprazole. The labeling was resolved as recommended in the approval letter.

IV. Phase IV Commitments: No phase IV Commitments or Risk Management Plans are required based upon review of this submission.

V. Pediatric Waiver Request: The Division recommends that the waiver request for the indication of reduction of risk of UGI bleeding in critically ill patients be denied. I am in agreement.

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/s/

Joyce Korvick
12/21/04 04:22:47 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: November 18, 2004

APPLICATION NUMBER: NDA 21-706

BETWEEN:

Santarus, Inc. Participant	Title
Christine Simmons, PharmD	Vice President, Regulatory Affairs
Gerald Proehl	President, CEO
Amanda Omlor	Electronic Publishing Associate, Regulatory Operations
Bonnie Hepburn, M.D.	Senior Vice President
Charles Davis	Senior Director, Regulatory Affairs

Phone Number: 858-314-5784

AND

Division of GI and Coagulation Drug Products (HFD-180) Participant	Title
Joyce Korvick, M.D.	Acting Director
Lolita Lopez, M.D.	Medical Reviewer
Marie Kowblansky, Ph.D.	Chemistry Reviewer
Sushanta Chakder, Ph.D.	Pharmacologist Reviewer
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Mushfiqur M. Rashid, Ph.D.	Statistical Reviewer
Ruyi He, M.D.	Medical Team Leader
Mary M. Lewis	Regulatory Project Manager
Melissa Hancock Furness	Regulatory Health Project Manager

SUBJECT: Labeling Review with Firm, #1

Background

Santarus, Inc. filed NDA 21-706 as an original new drug application on February 25, 2004, received on February 26, 2004, for Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg for the following indications: Short-term treatment (4-8 weeks) of active benign gastric

ulcer; and for [] of upper gastrointestinal bleeding in critically ill patients.

Today's Call

Mary Lewis opened the call with requesting introductions from the Agency and Santarus, Inc. This teleconference was to discuss the Agency mark-up labeling faxed to Santarus on November 12, 2004. Most deletions and changes made by the Agency were agreed upon by Santarus except for the following:

- Page 8 of 19 "Reduction of Risk of Upper Gastrointestinal Bleeding in Critically-Ill Patients", three-quarters down the page in the Deleted bubble, Santarus agreed to come up with a paragraph to describe the graphs that were removed.
- Page 14 of 19, in the first paragraph under the graph/table, the end of the last sentence the words "nosocomial pneumonia" will be added to the body systems on page 16. Santarus will remove our sentence ' [] J
- Page 15 of 19, the table "Number (%) of Critically-Ill Patients with Frequently Occurring Adverse Events by Body System and Preferred Term" the sponsor would like to keep the table as is. The Agency agreed to wait and see the table again after receipt from the sponsor's next edit.

At this time Marie Kowblansky, Chemist, informed Santarus that their expiry would likely be [] rather than the 24 months requested. Santarus stated that seemed reasonable.

Mary M. Lewis, RN, BSN
Regulatory Project Manager

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/s/

Mary Lewis
12/3/04 02:01:54 PM
CSO

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN
SERVICES

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

Date: November 18, 2004

From: Ruyi He, M.D.
Medical Team Leader, GI Team II
Division of Gastrointestinal and Coagulation Drug Products (HFD-
180)

Subject: NDA 21-706, submitted 2/26/04
Zegerid 40 mg (Omeprazole-Sodium Bicarbonate) powder for oral
suspension

The two proposed clinical indications are:

- short-term treatment (4-8 weeks) of active benign gastric ulcer, and
-  of upper gastrointestinal bleeding in critically ill patients

Applicant: Santarus Inc.

To: NDA 21-706

Background:

Zegerid is an immediate-release (ie, non-enterically coated) powder-for-suspension, containing 40 mg of omeprazole and 20 mEq (1680 mg) of sodium bicarbonate. NDA 21-636 for Zegerid 20 mg was approved on 6/15/04 for the following indications: 1) short-term treatment (4-8 weeks) of active duodenal ulcer, 2) treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), 3) short-term

treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy and 4) maintenance of healing of erosive esophagitis (EE).

In this NDA, Santarus is seeking approval of Zegerid 40 mg for short-term treatment (4-8 weeks) of active, benign gastric ulcer and for the prevention of upper gastrointestinal (GI) bleeding in critically ill patients. For the approval of Zegerid 40 mg for short-term treatment (4-8 weeks) of active, benign gastric ulcer, Santarus is relying on the safety and efficacy findings of the Agency from NDA 19-810 (Prilosec Delayed Release Capsules 20 mg and 40 mg) based on the 505(b)(2) regulations. Zegerid 40 mg is identical to the 20 mg dose strength except for omeprazole content. The indication prevention of upper GI bleeding in critically ill patients is a new indication that has not been approved before for any of the marketed PPIs, including omeprazole products. Data from a single clinical trial (OSB-IR-C03) was submitted in support of this indication. Study OSB-IR-C03 was conducted as a double-blind, double-dummy, multi-center, randomized, non-inferiority trial evaluating the effectiveness of Zegerid 40 mg delivered via nasogastric (NG) or orogastric (OG) tube compared to cimetidine I.V. 50 mg/hr in preventing UGI bleeding in patients at risk for stress-related mucosal damage. Currently, cimetidine I.V. is the only FDA approved therapy in preventing UGI bleeding in patients at risk for stress-related mucosal damage.

Study OSB-IR-C03

The OSB-IR-C03 trial was a double-blind, multicenter, randomized non-inferiority clinical trial comparing the effectiveness of Zegerid to the effectiveness of IV cimetidine in preventing UGI bleeding in patients at risk for stress related mucosal damage (SRMD). Participants in this trial were critically ill patients who had been admitted to a critical/intensive care unit and required mechanical ventilator support. Doses of oral suspensions were delivered through nasogastric (NG) or orogastric (OG) tubes. A total of 359 patients were enrolled in this study.

The primary efficacy endpoint of this trial was the occurrence of clinically significant UGI bleeding defined as: bright red blood per NG or OG tube that did not clear after NG or OG tube adjustment and 5 to 10 minutes of lavage with room temperature normal saline, or persistent Gastrocult®-positive coffee-ground material for at least eight consecutive hours in Day 1 and 2 (three consecutive gastric aspirates within 2 to 4 hours for Day 3 and 4) that did not clear with at least 100 mL of lavage with room temperature normal saline.

The results from OSB-IRC03 have shown that Zegerid was not inferior to continuous IV cimetidine with respect to the reduction of risk of clinically significant bleeding. There were 10 patients (10/181, 5.5%) in the cimetidine group and 7 patients (7/178, 3.9%) in the Zegerid group meeting the primary

endpoint. Demonstration of non-inferiority was made since the upper boundary of the confidence interval around the difference in rate was 2.8% for both the PP and ITT population, less than the prespecified non-inferiority margin of 5%.

In addition to the 17 patients who met the primary endpoint for clinically significant bleeding, 2 patients in the cimetidine group and 1 patient in the Zegerid group were withdrawn from the trial by the investigator because of clinically meaningful UGI bleeding. Significantly fewer Zegerid- treated patients (34, 19.1%) were found to have had at least one gastric aspirate containing blood compared to cimetidine-treated patients (58, 32%), $p=0.005$. Of the 15 patients who had 4 or more positive aspirates, only 3 were in the Zegerid treatment group. These results provide supportive evidence of the finding of the non-inferiority of Zegerid to cimetidine in preventing UGI bleeding in critically ill patients.

In addition, the median daily gastric pH in the Zegerid group was significantly higher than median daily gastric pH in the cimetidine group for each of the 14 days, and fewer patients in the Zegerid group required dose increases to keep the gastric pH above 4 (14.6% vs. 52.5%).

The safety experience in the trial (including deaths) reflected the severity of the underlying medical conditions of these critically ill patients. There were 48 deaths during the treatment period (27 in the Zegerid group and 21 in the cimetidine group), 43 deaths during the follow-up period (25 in the Zegerid group and 18 in the cimetidine group); none were considered to be related to trial drugs. The patients in the Zegerid group have higher mean APACHE II score compared to the cimetidine group (24.7 vs. 22.7) at the baseline. Moreover, patients who died in the Zegerid group had a mean APACHE II score of 28 at baseline compared to 24.2 in the cimetidine group, which may explain the numerically higher rate of mortality in the Zegerid group.

OSB-IR C07, an 8-week safety study conducted in patients with acid-related disorders shows that the safety profile of Zegerid 40 mg is similar to that of Prilosec 40 mg. In the

OSB-IR C03 trial conducted in critically ill patients, adverse events reported were similar in both treatment groups and were a reflection of the severity of the patients' underlying medical conditions. No new omeprazole-related safety issues were identified in association with Zegerid treatment of critically ill patients.

Clinical Pharmacology Studies

Data was submitted from two clinical pharmacology studies (OSB-IR-C05 and OSB-IR-C02) investigating the pharmacokinetics and pharmacodynamics of Zegerid 40 mg. Study OSB-IR-C02 evaluated the PK and pharmacodynamic (PD) profiles of omeprazole following administration of multiple 40 mg doses of Zegerid and Prilosec Delayed Release Capsule. As expected, Zegerid 40 mg was not bioequivalent to Prilosec delayed release capsules 40 mg. Although, AUC was similar, C_{max} was higher for Zegerid 40 mg (by 19.5% on day 1 and 51.1% on day 7). Despite the differences in pharmacokinetics, Zegerid and Prilosec Capsule were generally similar with respect to the pharmacodynamics of intragastric pH. Significant food-effect was observed for Zegerid with C_{max} and AUC decreasing by 60% and 27%, respectively following administration of 40 mg Zegerid 1 hour post-meal relative to administration 1 hour pre-meal. Study OSB-IR-C05 is an open label study that evaluated the safety and pharmacokinetics (PK) of two consecutive 40 mg doses of Zegerid administered within 6 hours of each other. C_{max} and AUC of omeprazole increased by 30% and 100%, respectively, following administration of a second 40 mg dose of Zegerid within 6 hours of a 40 mg dose of Zegerid, which is consistent with the increase in omeprazole systemic exposure observed following administration of Zegerid 40 mg for 7 days.

Office of Clinical Pharmacology and Biopharmaceutics recommend that NDA 21-706 be acceptable for both indications provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert (Clinical Pharmacology and Biopharmaceutics Review for NDA 21-706).

Conclusions and recommendations:

The sponsor has submitted one adequate and well-controlled clinical trial (OSB-IR-C03) in critically ill patients demonstrating effectiveness of Zegerid 40 mg administered through nasogastric (NG) or orogastric (OG) tubes for up to 14 days in reducing the risk of UGI bleeding. Safety of Zegerid 40 mg use in these patients is supported by OSB-IR-C03 and OSB-IR C07 (8 weeks safety study). Generally, the adverse event profile is similar to that in the current labeling for Zegerid or omeprazole. I recommend that this application be approved.

I concur with Dr. Lopez's recommendations for labeling changes (NDA 21-706 review by L. Lopez dated 11/12/04).

The sponsor's request to waiver Pediatric Studies should be denied for the indication of reduction of risk of UGI bleeding in critically ill patients. Similar to adults, children under physiologic stress can develop stress ulceration and acute UGI bleeding. The sponsor needs to conduct studies to provide information on the benefit of this drug in critically ill pediatric patients.

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/s/

Ruyi He
11/18/04 03:57:32 PM
MEDICAL OFFICER

FACSIMILE TRANSMITTAL SHEET

DATE: November 12, 2004

To: Christine Simmons	Fro Mary Lewis
Company: Santarus, Inc.	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (858) 314-5701	Fax number: 301-443-9285
Phone number: (858) 314-5731	Phone number: 301-827-7475
Subject : Proposed labeling mark-up, NDA 21-706.	

Total no. of pages including cover: 23

Comments: Please find attached our mark-up of your proposed labeling for NDA 21-706. We have scheduled a telecom with you for Thursday, November 18, 2004 from 2:00 to 3:00 P.M.

Document to be mailed: • YES ☒ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

ATTACHMENT:

23 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

 _____ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NOV - 2 2004

Food and Drug Administration
Rockville MD 20857

Benjamin Margolis, M.D
1 Erie Court, Suite 3000
Oak Park, IL 60302-2566

Dear Dr. Margolis,

Between June 14, and June 25, 2004, Ms Lisa Hayka, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation protocol # OSB-IR-C03 entitled: "A Comparison of Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension, to Intravenous Cimetidine for the Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients") of the investigational drug Rapinex (omeprazole IR 40 mg) oral suspension, performed for Santarus, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your response to the 483 dated July 23, 2004, addressed to Ms. Lisa Hayka, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Hayka presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

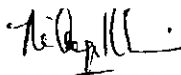
1. You did not promptly report serious adverse reactions to the sponsor (21 CFR 312.64(b)).
 - a. Subject 34508 expired on — and this was reported to the sponsor on . —
 - b. Subject 34525 expired on — and this was reported to the sponsor on —
 - c. Subject 34528 began trial drug on 2/28/03, experienced hepato-renal failure starting — and died on — This was reported to the sponsor on —
2. You did not ensure that the investigation was conducted according to the signed investigator statement and the investigational plan (21 CFR 312.60).
 - a. You administered prohibited medications to subjects treated on this protocol:
 1. Subjects # 34,550; 34,507; and 34,133 received a dose of Pepcid on Day 1.
 2. Subjects # 34,510 and 34,459 received magnesium oxide on several days during the study period.

- b. Gastric aspirate pH was not documented at all specified times for subjects # 34,510; 34,459; 34,361; 34,527; 34,563; 34,133; 34,134; 34,525; 34,460; 34,507; 34,527; 34,547; 34,433; 34,136, and 34,550.
- c. The second dose of oral study drug was not administered after the Day 1 initial dose for subjects # 34,361; 34,561; and 34,550.
- d. Subjects # 34,431; 34,432; and 34,433 signed a consent form version not approved by the IRB.
- e. The oral drug dosage was not increased for subject # 34,510 although the gastric pH was less than 4 on two occasions one hour apart, as required by the protocol.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEL. 2 3

Field Classification: OAI

Headquarters Classification:

- ☐ 1)NAI
☒ 2)VAI- no response required
☐ 3)VAI- response requested
☐ 4)OAI

If Headquarters classification is a different classification, explain why:

Although many violations are reported, they did not affect the validity of the data.

Deficiencies noted:

- ☒ inadequate informed consent form (03)
☒ failure to adhere to protocol (05)
☒ unapproved comitant therapy (07)
☒ failure to report ADRS (16)

Deficiency Codes: 3, 5, 7, and 16

cc:

HFA-224

HFD-180 Doc.Rm. NDA# 21,706

HFD-180 Review Div.Dir. Korvick

HFD-180 MO Lopez

HFD-180 PM Houstoun

HFD-46/47c/t/s/ GCP File # 11263

HFD-46/47 GCP Reviewer Malek

HFR-CE650 DIB Baumgarten

HFR-CE6520 Bimo Monitor Yuscus

HFR-CE6520 Field Investigator Hayka

GCF-1 Seth Ray

r/d: (REVIEWER): KM

reviewed:J.S.:

f/t:ml/sg:

o:\KM\Margolis

Reviewer Note to Rev. Div. M.O.

The field investigator reviewed the records of 17 subjects out of 50 randomized. Violations were reported which are: 1) The PI did not promptly report serious adverse events to the sponsor 2) Protocol violations: three subjects received Pepcid and 2 received magnesium oxide (prohibited medications); gastric aspirate pH was not recorded at all protocol specified times for some subjects; the second dose of oral study drug was not administered after the Day 1 initial dose for

Page 4- Dr. Margolis

three subjects; and oral study drug was not increased for one subject although the gastric pH was less than 4 on two occasions, one hour apart.

These violations would not affect the validity of the data, and the data from this study can be used in support of the NDA.

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/s/

Ni Aye Khin
11/3/04 12:01:14 PM

4 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/25/04

NDA 21-706

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
V.P., Regulatory Affairs and Quality Assurance
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Powder for Oral Suspension, 40mg.

We are reviewing the Chemistry, Manufacturing and Controls 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.

- Please lower the acceptance criterion for the unidentified omeprazole-related impurity with the relative retention time of 1.3. Once the structure of this impurity has been determined, the requested limit may be appropriate.
- Please add 1.3 testing to the drug product specification.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at 301-827-7475.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products,
HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
10/25/04 02:07:20 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/15/04

NDA 21-706

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
Vice President, Regulatory Affairs & Quality Assurance
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your February 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg.

We also refer to your submission dated April 22, 2004 that included a study report for trial OSB-IR CO3.

We are reviewing the Clinical section of your submission and have the following information requests with regard to Clinical Trial OSB-IR CO3. We request a prompt written response in order to continue our evaluation of your NDA.

There is a lack of consistency between the tables and appendices for the number of patients who died. Please provide a table for all patients who died during the treatment period and the follow-up period. The table should include the following information:

- The treatment drug
- Patient ID/Number
- Date of death
- Number of days on the treatment/drug
- Number of day(s) post last dose
- Cause of death
- Relationship to drug

In addition, please group the patients who died as follows:

- While on the trial drug and one (1) day post last dose
- Two to seven days post trial follow-up
- More than eight days post trial follow-up

If you have any questions, call Mary Lewis, Regulatory Project Manager, at 301-827-7475.

Sincerely,

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products,
Office of New Drugs, ODE III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
10/15/04 01:31:19 PM
Signing for Brian Strongin, CPMS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Steven A. Conrad, M.D., Ph.D.
Louisiana State University
1501 Kings Highway
Shreveport, LA 71103

AUG 18 2004

Dear Dr. Conrad:

Between June 10 and June 17, 2004, Ms. Carolyn E. Barney, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # OSB-IR-CO3 entitled: "A Comparison of Omeprazole Sodium Bicarbonate-Immediate-Release Powder for Suspension to Intravenous Cimetidine for the Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients") of the investigational drug Rapinex, performed for Santarus, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that, except for minor deficiencies, you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Barney during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Joseph P. Salewski
Joseph Salewski

Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEL: ☒ J

Field Classification: NAI

Headquarters Classification:

☒ 1)NAI

☐ 2)VAI- no response required

☐ 3)VAI- response requested

☐ 4)OAI

cc:

HFA-224

HFD-180 Doc.Rm. NDA# 21-706

HFD-180 Review Div.Dir. Justice

HFD-180 MO Lopez

HFD-180 PM Houstoun

HFD-46/47c/r/s/ GCP File # 11233

HFD-46/47 GCP Reviewer Malek

HFR-SE450 DIB Herd

HFR-SE450 Bimo Monitor Roosevelt

HFR-SE4555 Field Investigator Barney

HFR-SE450 DDs Thornburg

GCF-1 Seth Ray

r/d: (REVIEWER): KM-8-5-04

reviewed: JS:

f/t:ml/sg:

o:\filename\document name O:\KM\Conrad

Reviewer Note to Rev. Div. M.O.

The field investigator reviewed the records of all 26 subjects enrolled in the study. The PI discontinued two subjects from the study (# 399 & 404). # 399 was discontinued due to continuing and extremely low pH results despite increasing dose. # 404 was discontinued due to active bleeding after two hours. The field investigator did not report any GCP violations in this study.

The data from this study can be used in support of the NDA supplement.

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/s/

Joseph Salewski
8/24/04 03:13:04 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: August 25, 2004

To: Christine Simmons	From: Mary Lewis
Company: Santarus, Inc.	Division of Gastrointestinal & Coagulation Drug Products
Fax number: (858) 314-5701	Fax number: 301-443-9285
Phone number: (858) 314-5731	Phone number: 301-827-7475
Subject: NDA21706 Email question of 8/19/04 from C. Simmons	

Total no. of pages including cover: 4

Comments:

Please find our response (Attachment II) to your question from your 8/19/04 email (Attachment I).

Document to be mailed: • YES ☒ NO

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Attachment I

**NDA 21-706 Zegerid (omeprazole) Powder for Oral Suspension, 40 mg
Santarus**

Mary,

Update

FYI, we are in the process of updating the Zegerid Powder for Oral Suspension package insert that was submitted in the 40 mg NDA (NDA 21-706) to reflect the changes that were made as part of the Zegerid 20 mg NDA (NDA 21-636) approval process. I'm hoping to send it to you next Friday.

Question

We are also wondering whether we should combine the suspension, capsule and tablet products in one package insert or have separate package inserts. Does the Agency have a position on this?

Christine

Christine Miller Simmons, Pharm.D
Vice President, Regulatory Affairs & Quality Assurance
Santarus, Inc
10590 West Ocean Air Blvd Suite 200
San Diego, CA 92130

Phone: 858-314-5731
Cell: 858-229-4772
Fax: 858-314-5705
Email: csimmons@santarus.com
Website: www.santarus.com

Attachment II

FDA Response:

The 40 mg NDA (NDA 21-706), is Powder for Oral Suspension only, there is no data about capsule and tablet products. Therefore, you should not combine the suspension, capsule and tablet products in one package insert at this time.

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/s/

Mary Lewis
8/25/04 03:41:06 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Andrea Gabrielli, M.D.
1600 SW Archer Road
University of Florida
Gainesville, FL 32610

AUG 17 2004

Dear Dr. Gabrielli:

Between June 9 and June 14, 2004, Ms. Barbara T. Carmichael, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # OSB-IR-C03 entitled: "A Comparison of Omeprazole Sodium Bicarbonate-Immediate Release Powder for Oral Suspension, to Intravenous Cimetidine for the Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients") of the investigational drug Rapinex (omeprazole IR 40 mg) for oral suspension, performed for Saunters, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, your June 15, 2004 response to the 483, and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Carmichael presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not report a serious adverse event in a timely manner to the sponsor and IRB, as required by Federal regulations [21 CFR 312.64]

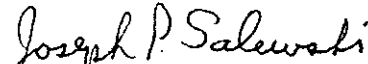
Subject # 101 expired on — and was reported to the sponsor on —

2. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]
 - a. Subjects # 105 and 106 were given each other's dose. 105 was on the investigational drug and subject 106 was on cimetidine.
 - b. Subject # 102 received increased IV dose and an additional oral dose of study drug due to incorrect interpretation of pH assessment.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Carmichael during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

A handwritten signature in cursive script that reads "Joseph P. Salewski".

Joseph Salewski.

Acting Branch Chief

Good Clinical Practice Branch I, HFD-46

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

CFN/FEL. ☒ 3
Field Classification: VAI
Headquarters Classification:

☐ 1)NAI
☒ 2)VAI- no response required
☐ 3)VAI- response requested
☐ 4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted: (Delete any that don't apply!)

X ☐ failure to report ADRS (16)

X ☐ other (18; please specify: Failure to properly administer the investigational drug)

Deficiency Codes: 16 & 18

cc:

HFA-224
HFD-180 Doc.Rm. NDA# 21-706
HFD-180 Review Div.Dir Justice.
HFD-180 MO Lopez
HFD-180 PM Houstoun
HFD-46/47c/r/s/ GCP File # 11528
HFD-46/47 GCP Reviewer Malek
HFR-SE200 DIB Gallant
HFR-SE250 Bimo Monitor Torres
HFR-SE250 Field Investigator Carmichael
GCF-1 Seth Ray
r/d: (REVIEWER): KM-8/04/04
reviewed:JS:
f/t:ml/sg:
o:\filename\document name

Reviewer Note to Rev. Div. M.O.

The field investigator reviewed the records of six subjects out of 25 enrolled in the study, which were : # 101, 107, 208, 210, 439, and 297. At this site only four subjects out of the 25 enrolled completed 14 days of medication. Few violations were found: subject # 101 died on — ' but was reported after 3 day; subjects 105 & 106 were given each other's dose once; and subject # 102 received an additional dose due to incorrect interpretation of pH assessment.

These violations would not affect the validity of the data and the data from this study can be used in support of the NDA

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/s/

Joseph Salewski
8/24/04 03:14:31 PM

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/26/04

NDA 21-706

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your February 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg.

We are reviewing the Statistical section of your submission and have the following information requests:

- Please clarify which .xpt (SAS) file is the primary efficacy data set.
- Please specify the name of the primary efficacy variable in the data set.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at 301-827-7475.

Sincerely,

{See appended electronic signature page}

Brian Strongin
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
7/26/04 04:34:32 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/6/04

NDA 21-706

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Christine Simmons, Pharm.D.
V.P., Regulatory Affairs and Quality Assurance
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your February 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests:

Please amend your application to include the pertinent CMC information that was needed for approval of NDA 21-636 (20 mg product).

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at 301-827-7475.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug
Products, HFD-180
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
7/6/04 03:40:24 PM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: May 18, 2004	DESIRED COMPLETION DATE: June 4, 2004	ODS CONSULT#:
DATE OF DOCUMENT: May 11, 2004	PDUFA DATE: June 15, 2004	04-0154

TO: Robert Justice, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH: Susan Daugherty
Project Manager
HFD-180

PRODUCT NAME:
Zegerid
Omeprazole Powder for Oral Suspension 20 mg

NDA SPONSOR:
Santarus, Inc.

NDA#: 21-636

SAFETY EVALUATOR: Denise P. Toyer, PharmD.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Zegerid. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DDMAC finds the proprietary name Zegerid acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 8, 2004

NDA#: 21-636

NAME OF DRUG: **Zegerid**
(Omeprazole Powder for Oral Suspension)
20 mg

NDA HOLDER: Santarus, Inc

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), for assessment of the proprietary name, "Zegerid" regarding potential name confusion with other proprietary and established drug names. This is the third proprietary name submitted by the sponsor for this product. The previous names Acitrel and Rapinex were not recommended for use by DMETS for the following reasons. Acitrel was thought to have potential orthographic and phonetic similarity to Acthrel and Accupril, while Rapinex was thought to have orthographic similarity to Regranex. The sponsor also submitted a trademark evaluation conducted by [redacted] for Zegerid. Revised container labels, carton and insert labeling were not submitted for review and comment at this time.

PRODUCT INFORMATION

Zegerid is indicated for use in the following:

1. Short-term treatment of active duodenal ulcer
2. Treatment of GERD
 - a. *Symptomatic GERD* – treatment of heartburn and other symptoms associated with GERD
 - b. *Erosive Esophagitis* – short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy
3. Maintenance of healing of erosive esophagitis

Zegerid contains the active ingredient Omeprazole. It will be available in single packets containing an oral powder for reconstitution. When mixed with water, the oral powder forms an oral suspension containing 20 mg of Omeprazole. The recommended usual dose is 20 mg per day. Zegerid will be marketed in cartons containing 30 packets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Zegerid to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Zegerid. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name Zegerid acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Zegerid. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, Drugs@FDA, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> and the electronic online version of the FDA Orange Book..

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Zegerid	Omeprazole Oral Powder for Suspension 20 mg	20 mg QD	N/A
Synercid	Quinupristin 150 mg and Dalfopristin 350 mg Supplied as 500 mg Injection Diluted in 5% Dextrose Injection and infused over 60 minutes	7.5 mg/kg every 8 to 12 hours depending upon dose	SA/LA
Tegretol	Carbamazepine Chewable Tablets 100 mg Tablets 200 mg Suspension 100 mg/5 mL and 200 mg/10 mL	800 mg to 1200 mg per day in divided doses	LA
Vepesid	Etoposide Capsules 50 mg Injection 20 mg/mL Lyophilized Powder for Injection	Testicular cancer (parenteral): Usual dose is 50 to 100 mg/m ² /day on days 1 to 5 to 100 mg/m ² /day on days 1, 3 and 5. Small Cell Lung Cancer (parenteral): 35 mg/m ² /day for 4 days to 50 mg/m ² /day for 5 days. Courses are repeated at 3- to 4-week intervals after recovery from toxicity. (Oral): 2 times the IV dose rounded to the nearest 50 mg.	SA/LA
Zerit	Stavudine Capsules 15 mg, 20 mg, 30 mg and 40 mg Powder for Oral Solution 1 mg/mL when reconstituted	One capsule every 12 hours	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Zegerid were discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Zegerid with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to

simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zegerid (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> <i>Zegerid</i> <i>300 mg po qid</i> <i>#30</i>	Zegerid number 30 one daily with two refills
<u>Inpatient RX:</u> <i>Zegerid 1 po qd #30</i> <i>2/11/11 11:00 AM</i>	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies

E. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and Sound-Alike Concerns

In reviewing the proprietary name Zegerid, the primary concerns raised were related to potential confusion with currently marketed products Synercid, Tegretol, Vepesid, and Zerit.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Zegerid could be confused with currently marketed products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Zegerid.

- a. Zegerid and Synercid may sound-alike when spoken and look-alike depending upon how they are scripted. Synercid is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant enterococcus faecium bactremia and complicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible) or Streptococcus pyogenes. The names have three syllables and begin with letters (Z vs. S) which may look similar when scripted (see page 6). Both names have a downstroke letter near the beginning and share the last two letters (id). These characteristics contribute to the look-alike similarities between these two names. The sound-alike similarities stem from the beginning letters (Z vs. S) and the ending letters

(erid vs. ercid). Although the second syllable of Zegerid begins with the letter 'g' which produces a hard 'ger' sound when combined with the next two letters, this may not distinguish the two names. Despite these similarities the products differ with respect to the route of administration (oral vs. intravenous), formulation (tablet vs. powder for reconstitution), dosing interval (daily vs. every 8 to 12 hours) and dose (20 mg vs. 7.5 mg/kg). Although the doses could potentially overlap for a 2.7 kilogram pediatric patient, Synercid is not currently approved for use in the patient population and only limited studies have been conducted. Overall the product characteristics, especially strength, help to differentiate Zegerid and Synercid and may help to decrease the potential for name confusion between these two products.

Synercid
Zegerid

- b. Tegretol and Zegerid may look similar depending upon how they are scripted. Tegretol is indicated for the treatment of partial seizures with complex symptoms and for the treatment of pain associated with true trigeminal neuralgia. The names share the letters 'eg' within the first syllable and have an upstroke and downstroke in a similar position (g vs. g and l vs. d). However, Tegretol has an additional upstroke at the beginning of the third syllable, which may help to distinguish the names when scripted. The products also have different product characteristics such as dosing interval (2 to 4 times a day vs. daily) and strength (100 mg and 200 mg vs. 20 mg). Although, the strength of the two products is different the products share similar numerals (200 vs. 20) and a Zegerid 20 mg dose could be misinterpreted as 200 mg if written with a trailing zero and indistinguishable decimal point. However, the different dosing intervals will help to differentiate these two names. The lack of convincing orthographic similarities and the different dosing frequencies decreases the potential for name confusion between Tegretol and Zegerid.

Tegretol
Zegerid

- c. Vepesid and Zegerid may look-alike and sound-alike depending upon how they are scripted and/or pronounced. Vepesid is indicated for the treatment of testicular cancer and small cell lung cancer. The beginning letters (V vs. Z) may look similar when scripted and the remaining letters (epesid vs. egerid) are also orthographically similar (see below). The greatest contribution to the sound-alike similarity is that they share the same vowel sound (short e) in the first syllable and have phonetically similar sounds (eh sid vs. eh rid) in the last two syllables. The greatest potential for confusion is between Vepesid oral capsules and Zegerid tablets. However, these products have different doses (20 mg vs. 50 mg/m²/day) and duration of therapy. Since the dose of Vepesid capsules is two times the dose of Vepesid injectable, the potential for overlapping doses between Vepesid capsules and Zegerid is minimal. Additionally, Vepesid will be given for five days whereas Zegerid may be given indefinitely for a chronic condition. Despite the orthographic similarities the different dosing for Vepesid and Zegerid decreases the potential for name confusion between these two products.

Zegerid
Vepesid

- d. Zerit and Zegerid may sound similar depending upon how they are pronounced. Zerit is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. The phonetic similarity of this name pair is attributed to the fact that both names begin with the same letters (Ze) and end with similar sounding letters (rit vs. rid). If the second syllable is not differentiated when pronounced, then the names may sound similar. However, Zegerid has three syllables whereas Zerit has only two syllables. Even when the names are pronounced very fast, it is difficult not to hear the second syllable. They have different dosing intervals (daily vs. every 12 hours) which may help to distinguish the two products. Although the products share the same dosage form (oral powder for reconstitution), Zerit will usually be reconstituted by the pharmacist prior to dispensing whereas each dose of Zegerid is dissolved in water by the patient. This difference may also help the healthcare practitioner if the prescription is written or stated in teaspoons instead of milligrams. Additionally, the recommended adult dose is 40 mg BID for patients weighing greater than 60 kilograms and 30 mg BID for patients weighing less than 60 kilograms. Zerit 20 mg is generally reserved for patients with renal failure, on hemodialysis, or patients being restarted on Zerit after the development of peripheral neuropathy. Since monotherapy is not recommended in HIV-1 treatment, Zerit is unlikely to be prescribed alone but will generally be prescribed with other HIV drugs. Therefore, the availability of other information (e.g., either new prescription for another HIV-1 drug or other HIV-1 drugs currently on their pharmacy record) may also help when trying to differentiate these two products and minimize the potential for name confusion.

2. [J Independent Name Review

On behalf of Santarus, Inc. [J conducted a trademark evaluation of the proposed name Zegerid. The participants in their evaluation identified twenty product names as having the potential to look or sound similar to Zegerid. The names were: Degas, Lisinopril, Pepcid, Reminyl, Rid, Synercid, Tagamet, Tegaserod, Tegretol, Xigris, Zebeta, Zelnorm, Zerit, Zestoretic, Zestril, Zocor, Zolof, Zonegran, Zyprexa, and Zyrtec. A complete listing of the names and number of respondents can be found in Appendix B. Seven of these proprietary names were noted more than once as a potential look and/or sound-alike to Zegerid. These include [sound-alike]: Zelnorm (2), Zocor (2), Zerit (2), Rid (3), Synercid (3), and [look-alikes]: Tegretol (7) and Zestril (11). DMETS reviewed three of these names: Zerit, Synercid, and Tegretol (See section E-1 above). Since multiple responses were identified for the remaining products, the product characteristics for Zelnorm, Zocor, Rid, and Zestril can be found below in Table 2 (see page 8).

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Table 2.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other*
Zegerid	Omeprazole Oral Powder for Suspension 20 mg	20 mg Orally Daily	N/A
Zelnorm	Tegaserod Tablet 2 mg and 6 mg	6 mg Orally Two Times a day	S/A
Zocor	Simvastatin Tablets 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg	20 mg Orally Daily Range: 5 mg to 80 mg Daily	S/A
Rid	Shampoo: 0.33% pyrethrins, 4% piperonyl butoxide Mousse: 0.33% pyrethrins, 4% piperonyl butoxide	For mousse: thoroughly wash affected areas with warm water and soap or regular shampoo. For shampoo: Use a small amount of water to work shampoo into the hair and scalp or skin until a lather forms. Rinse	S/A
Zestril	Lisinopril Tablets 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg	10 mg Daily Range: 20 mg to 40 mg Daily	SA/LA

[] determined that the orthographic and/or phonetic properties and the product characteristics (mode of administration, formulation, and dosing regimen) of all twenty products identified in their evaluation as potential look and/or sound-alike products to Zegerid are unique enough that they would be unlikely to be confused with the proposed trade name, Zegerid. DMETS also reviewed the orthographic/phonetic similarities and the characteristics of the products listed in [] review and concur with [] conclusion that the potential for confusion between Zegerid and the aforementioned names is minimal.

III. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Zegerid. DMETS considers this a final review. However, if the approval of this NDA is delayed beyond 90 days of the signature date of this review then the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DDMAC finds the proprietary name, Zegerid acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Denise P. Toyer, PharmD.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Addendum November 19, 2004: This proprietary name review was conducted for NDA 21-636 Zegerid 20 mg which was approved on 6/15/04. Since the NDA 21-706 only provides for an additional strength (40 mg), DMETS will not re-review the proprietary name Zegerid. Please feel free to consult DMETS, if you would like us to review the labels and labeling for Zegerid 40 mg.

APPENDIX A

VOICE	INPATIENT	OUTPATIENT
Celurid	Zagarid	Zeberid
Dagarid	Zagerid	Zegerid
Sagarid	Zegerid	Zegerid
Sagarit	Zegerid	Zegerid
Segarid	Zegerid	Zegerid
Zagared	Zegerid	Zegerid
Zagared	Zegerid	Zegerid
Zagarid	Zegerid	Zegerid
Zagarid	Zegerid	Zegerid
Zagarid	Zegerid	Zegerid
Zagavid	Zegerid	Zegerid
Zegarid	Zegerid	Zegerid
Zegarid	Zegerid	Zegerid
Zegavid	Zegerid	Zegerid
Zegulid	Zegerid	Zegerid
Zegurade	Zegesid	Zegerid
	Zegrid	Zegerid
	Zigerid	Zegerid
	Zigerid	Zegexid
	Zigesid	Zegrid

APPENDIX B

Product Name	Sound-Alike (Respondent #)	Look-Alike (Respondent #)
Rid	3	
Synercid	3	
Zelnorm	2	1
Zocor	2	1
Zerit	2	
Zyrtec	1	1
Degas	1	
Tegaserod	1	1
Zebeta	1	
Zonegran	1	
Zestril	1	11
Xigris	1	
Tegretol		7
Zyprexa		1
Zestoretic		1
Reminyl		1
Lisinopril		1
Tagamet		1
Zoloft		1
Pepcid	1	

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

/s/

Denise Toyer

11/19/04 03:02:41 PM

DRUG SAFETY OFFICE REVIEWER

See Addendum on Page 8. This proprietary name review
was conducted for NDA 21-636 Zegerid 20 mg
which was approved on 6/15/04. Since the NDA
21-706 only provides for an additional strength (40
mg), DMETS will not re-review the proprietary name
Zegerid.

3 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

5/27/04

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-706

Name of Drug: Omeprazole Power for Oral Suspension 40 mg (Trade name – TBD)

Sponsor: Santarus, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Electronic

Submission Date: February 25, 2004

Receipt Date: February 26, 2004

Filing Date: April 26, 2004

User-fee Goal Date(s): August 26, 2004 (P)
December 26, 2004 (S)

Proposed Indication: Short-term treatment (4-8 weeks) of active benign gastric ulcer and
[] of upper gastrointestinal bleeding in critically ill patients

Other Background Information: This is a 505(b)(2) application and the sponsor is requesting a priority review. IND 46,656, submitted on November 10, 1994, to study the use of a simplified omeprazole suspension (omeprazole bicarbonate solution) in the prophylaxis of stress-related mucosal damage. NDA 21-636, submitted on August 15, 2003, for Omeprazole Powder for Oral Suspension 20 mg, indicated for short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis. Proprietary names were submitted to IND 46,656, omeprazole powder for oral suspension. A letter was sent informing the company that they would need to submit new proprietary names.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		
2. Form FDA 356h (original signature)	X		
a. Establishment information	X		Submitted on attached document entitled "Establishment Information, Supplement to Form FDA 356h" on Page 1 in volume 1
b. Reference to DMF(s) & Other Applications	X		
3. User Fee FDA Form 3397	X		User fee payment verified 2/24/04
4. Patent information & certification	X		Listed in sections 1.3.1 and 1.3.2
5. Debarment certification (Note: Must have a definitive statement)	X		Listed in section 1.3.3
6. Field Copy Certification	X		Listed in section 1.3.4
7. Financial Disclosure	X		Listed in section 1.3.6
8. Comprehensive Index	X		Listed in section 1.3 and electronically
9. Pagination	X		Section and page # located in upper right hand corner. Modules are listed under the summary section of the TOC.
10. Summary Volume	X		
11. Review Volumes	X		Available on \CDSESUB1\N21706\N_000\2004-02-25
12. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Listed in section 1.4.1
b. annotated PI	X		Listed in section 1.5

c. immediate container	X		Listed in section 1.4.2 and 1.4.3 (professional sample)
d. carton	X		Listed in section 1.4.4
e. patient package insert (PPI)		X	
f. foreign labeling (English translation)		X	
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Available electronically
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Available electronically

Y=Yes (Present), N=No (Absent)

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PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Under section 2.5.1 (module 5) of summary
2. Foreign Marketing History		X	
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Under section 2.3 (of module 3) of summary
b. Nonclinical Pharmacology/Toxicology			N/A
c. Human Pharmacokinetic & Bioavailability	X		Under section 2.5.3 (of module 5) of summary
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis		X	
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Under section 2.5.6
5. Summary of Safety	X		Under section 2.7.4
6. Summary of Efficacy	X		Under section 2.7.3

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Sent in April 22, 2004, available in EDR April 23, 2004

2. Controlled Clinical Studies		N/A
a. Table of all studies	x	Under section 2.5.4
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x	List of investigators not provided
c. Optional overall summary & evaluation of data from controlled clinical studies	x	
3. Integrated Summary of Efficacy (ISE)	x	
4. Integrated Summary of Safety (ISS)	x	
5. Drug Abuse & Overdosage Information		N/A
6. Integrated Summary of Benefits & Risks of the Drug	x	
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	x	Table 2.5.3-5

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	x		Sponsor sent in pediatric waiver request March 22, 2004
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in	x		

MS WORD			
b. Stability data in SAS data set format (only if paper submission)			N/A
c. Efficacy data in SAS data set format (only if paper submission)			N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)			N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)			N/A
3. Exclusivity Statement (optional)	X		

Y=Yes (Present), N=No (Absent)

Conclusions: This NDA is fileable. At the filing meeting it was decided that this application would be a standard review.

Name: Monika Houstoun
Regulatory Project Manager

cc:

Original NDA
HFD-180/Div. Files
HFD-180/RPM
ADMINISTRATIVE REVIEW

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 26, 2004

BACKGROUND: IND 46,656, submitted on November 10, 1994, to study the use of a simplified omeprazole suspension (omeprazole bicarbonate solution) in the prophylaxis of stress-related mucosal damage. NDA 21-636, submitted on August 15, 2003, for Omeprazole Powder for Oral Suspension 20 mg, indicated for short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis. Santarus submitted NDA 21-706 on February 25, 2004, we received it on February 26, 2004 for Omeprazole Powder for Oral Suspension 40 mg, indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer and $\square$ of upper GI bleeding in critically ill patients. This is a 505(b)(2) application and it was submitted electronically. The sponsor is requesting a priority review for this application.

ATTENDEES: Robert Justice, Joyce Korvick, Ruyi He, Lolita Lopez, Jasti Choudary, Liang Zhou, Marie Kowblansky, Stella Grosser, Khairy Malek, Sushanta Chakder, Suliman Al-Fayoumi, Susan Daugherty, Monika Houstoun

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical: Lolita Lopez

Statistical: Stella Grosser will email me with name of the reviewer

Pharmacology: Sushanta Chakder

Chemistry: Marie Kowblansky

Environmental Assessment (if needed):

Biopharmaceutical: Suliman Al-Fayoumi

DSI: Khairy Malek

Regulatory Project Management: Monika Houstoun

Other Consults: DMETS, DDMAC

Per reviewers, are all parts in English or English translation?

☒ YES

NO

CLINICAL

FILE X

REFUSE TO FILE

- Clinical site inspection needed: X YES NO
- Advisory Committee Meeting needed? YES, date if known X NO
- 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? X N/A YES NO

CLINICAL MICROBIOLOGY NA X FILE

REFUSE TO FILE

STATISTICS	FILE <u> X </u>	REFUSE TO FILE <u> </u>
BIOPHARMACEUTICS	FILE <u> X </u>	REFUSE TO FILE <u> </u>
PHARMACOLOGY	NA <u> X </u> FILE <u> </u>	REFUSE TO FILE <u> </u>

- No PT information was submitted for review, but PT will be involved in label discussion

CHEMISTRY	FILE <u> X </u>	REFUSE TO FILE <u> </u>
-----------	-------------------	------------------------------

- | | | |
|--|-----|-----------------|
| • Establishment(s) ready for inspection? | YES | NO |
| • Microbiology | YES | <u> X </u> NO |

ELECTRONIC SUBMISSION: Yes

Any comments: Lolita Lopez recommended denial of priority review status, since there is another agent, IV cimetidine, with that indication. After some discussion, it was decided deny the priority review request. It was also discussed that the sponsor only conducted one clinical trial for this NDA and we normally require 2. It was decided that this was a review issue and not a filing issue, however, it was decided to mention this to them in the 74 day filing letter.

REGULATORY CONCLUSIONS/DEFICIENCIES:

 The application is unsuitable for filing. Explain why:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 No filing issues have been identified.

 X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Monika Houstoun, Regulatory Project Manager, HFD-180

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/s/

Monika Houstoun

5/27/04 02:49:59 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-706

5/6/04

Santarus, Inc
Attention: Christine Simmons, Pharm.D.
Vice President, Regulatory Affairs and
Quality Assurance
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

Please refer to your February 25, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg.

We also refer to your submissions dated March 22, 2004, March 30, 2004, and April 22, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 26, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

A single study was submitted. More than one study is usually required for approval. Please refer to the guidance titled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May, 1998)."

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

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

NDA 21-706

Page 2

If you have any questions, call Monika Houstoun, Pharm.D., Regulatory Project Manager, at (301) 827-9333.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
5/6/04 09:19:53 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-706

4-7-04

Santarus, Inc
Attention: Christine Simmons, Pharm.D.
Vice President, Regulatory Affairs and
Quality Assurance
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Dr. Simmons:

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

Name of Drug Product: Omeprazole Immediate-Release Powder for Oral Suspension, 40 mg

Review Priority Classification: Standard (S)

Date of Application: February 25, 2004

Date of Receipt: February 26, 2004

Our Reference Number: NDA 21-706

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 26, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 26, 2004.

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-706

Page 2

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Attention: Division Document Room, 8B-45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call me at (301) 827-9333.

Sincerely,

/s/ [See appendix for electronic signature page]

Monika Houstoun, Pharm.D.

Regulatory Project Manager

Division of Gastrointestinal and

Coagulation Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Monika Houstoun
4/7/04 11:34:22 AM

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 30, 2001
Time: 12:30 p.m. - 2:00 p.m.
Location: Parklawn Building, Chesapeake Conference Room

Application: IND 46,656
Omeprazole Sodium Bicarbonate – immediate release, powder for suspension (OSB-IR(PWD

Meeting Chair: Joyce Korvick, M.D., Deputy Director, HFD-180

Meeting Recorder: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

Attendees:

Santarus, Inc.

Bonnie Hepburn, M.D, Vice President, Drug Development
Debra Gessner, Director, Regulatory Affairs
Robert Bagin, Ph.D. Director, Biostatistics and Data Management
Gerald Proehl, President and Chief Operating Officer
J Consultant, J
J Consultant, J

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Joyce Korvick, M.D., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader
Liang Zhou, Ph.D., Chemistry Team Leader
Arthur Shaw, Ph.D., Chemistry Reviewer
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Pharmacological Evaluation II (HFD-870)

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader
Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics (HFD-715)

Thomas Permutt, Ph.D., Statistics Team Leader

Office of Generic Drugs (HFD-604)

Donald Hare

Background: IND 46,656 was submitted by Michael Metzler, M.D., University of Missouri, on November 10, 1994 to study the use of a simplified omeprazole suspension (SOS) (omeprazole bicarbonate solution) in the prophylaxis of stress-related mucosal damage. In late 1995, Dr. Metzler began studying a flavored SOS (Chocobase) for pediatric gastroesophageal reflux disease (GERD).

Meeting Minutes

Page 2

Dr. Metzler transferred ownership of this IND to Santarus, Inc. on January 31, 2001 for commercial development of SOS.

Santarus, Inc. submitted a meeting request and background package, dated August 31, 2001, for the purpose of discussing the clinical development plan for omeprazole sodium bicarbonate – immediate release, powder for suspension [OSB-IR (PWD —)]. The powder formulation will be suspended in water before administration. The sponsor plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study comparing OSB-IR (PWD — to the listed drug product, Prilosec (omeprazole) Delayed-Release Capsules. The sponsor also plans to conduct a clinical study comparing OSB-IR (PWD — to intravenous cimetidine to support a new indication for the treatment of upper gastrointestinal bleeding in critically ill patients. Protocol summaries of both studies were included in the background package.

Once the PK/PD and clinical studies are completed, Santarus, Inc. plans to submit a 505(b)(2) new drug application (NDA) also referencing FDA's findings concerning the safety and efficacy data contained in the NDA for Prilosec Delayed-Release Capsules.

Meeting objective: To discuss the clinical development plan for OSB-IR (PWD —

Meeting summary:

The sponsor presented a brief description of the company and its activities, a brief history of the development of SOS and OSB-IR, the proposed regulatory strategy for submission of a NDA, and an outline of the agenda for today's meeting.

Each agenda item below includes the sponsor's written question and the Agency's written response followed by an oral discussion.

Agenda items:

Biopharmaceutics (Protocol OSB-IR-CO2)

“A Comparison of the Pharmacokinetics and Pharmacodynamics of Omeprazole Sodium Bicarbonate-Immediate-Release (OSB-IR) Administered as a Liquid and Omeprazole Delayed-Release (OME-DR) Administered as a Solid Dosage Form (Prilosec®), in Healthy Subjects.”

1. Does the Agency concur with the proposed endpoints and analysis plan for the OSB-IR-CO2 trial?

Agency Response:

The proposed endpoints and analysis plan for study OSB-IR-CO2 are not acceptable. You should include C_{max} alongside AUC as the primary endpoints.

Discussion:

The sponsor plans to collect data on C_{max} for OSB-IR (PWD — but anticipates that it will be higher than that of Prilosec (approximately 50-60% higher after a single dose). The sponsor anticipates that the AUC of OSB-IR (PWD — will be similar to that of Prilosec. It is the sponsor's position that pharmacological effect is a function of the AUC rather than the C_{max} and that the pharmacodynamic (PD) data evaluating gastric acid suppression will support the pharmacokinetic (PK) data.

The Agency said that although the literature suggests that for proton pump inhibitors, AUC may be the best parameter to correlate with intragastric pH, there is not enough data on C_{max} to conclude that AUC is more important than C_{max} in evaluating the pharmacological effect of these drugs. Therefore, both parameters must be critically evaluated to determine whether the proposed drug product is bioequivalent to Prilosec.

The Agency also said that no well-established correlation exists between intragastric pH and clinical effect (i.e. healing or maintenance of healing of esophageal or gastroduodenal ulcers). Therefore, PD data alone cannot be relied upon to demonstrate efficacy of the proposed drug product in the event that bioequivalence to Prilosec cannot be established (this point is also discussed under #2 and #3 below).

2. If the AUC of omeprazole delivered as OSB-IR (PWD — at steady state is comparable to the AUC of omeprazole delivered as Prilosec at steady state (i.e. bounds of the 90% confidence interval for the ratio of test to reference are within 80-125%), may Santarus reference the safety database of Prilosec to support the OSB-IR (PWD — NDA?

Agency Response:

You may reference the Agency's finding that Prilosec is safe if both C_{max} and AUC are comparable across formulations (i.e. C_{max} and AUC for OSB-IR are either bioequivalent or of lower values relative to those of Prilosec). If C_{max} and AUC are lower, efficacy will need to be addressed appropriately.

3. If both formulations are comparable with regard to integrated gastric acidity at steady state (i.e. bounds of the 90% confidence interval for the ratio of test to reference are within 80-125%), may Santarus reference efficacy data previously submitted in the Prilosec NDA, in order to include indications from the Prilosec label in the OSB-IR (PWD — label?

Agency Response:

Currently, no well-established link has been demonstrated between elevation of intragastric pH and healing or maintenance of healing of gastric or esophageal ulcers. Hence, efficacy data may not be referenced from that of Prilosec solely based on PD data.

Comparative PD data may serve as supportive evidence during the NDA review.

Discussion:

The Agency reiterated its position that in the event that bioequivalence between the proposed drug product and Prilosec cannot be established based upon C_{max} and AUC, the Agency's findings concerning the clinical data contained in the NDA for Prilosec may not be referenced based on the PD data alone. Additional efficacy data must be submitted to support inclusion in the proposed package insert of each approved indication for Prilosec.

4. Does the Agency agree that due to the known variability of omeprazole blood levels with regard to C_{max} , the C_{max} for each formulation will be assessed but will not be included as an endpoint?

Agency Response:

No. Based on the Agency's experience, bioequivalence on both C_{max} and AUC has been successfully demonstrated for omeprazole formulations. You should include C_{max} in your PK analysis.

In addition, we request you conduct the following studies:

- Food-effect study on the 40 mg dosage strength.
- Single dose bioequivalence (BE) study for the 20 mg dosage strength.

Also, you should conduct appropriate studies to support the dosing regimen for the proposed new indication ζ I .

Discussion:

Regarding the recommended food-effect study, the sponsor asked if the proposal to administer the proposed drug product to healthy volunteers in a fasted condition but not fasted for 24 hours is sufficient. The Agency recommended administering the drug following a high fat meal

to test the worst-case scenario.

Regarding the recommended BE study, the sponsor said it does not currently plan to develop a 20 mg strength but will consider doing so if a 20 mg strength is required for inclusion in the proposed package insert of the approved indications for Prilosec. The sponsor pointed out that FDA guidance indicates that bioequivalence studies may be conducted with the highest approved dose, in this case, 40 mg. The Agency said the guidance does not apply in this case because these two strengths of omeprazole are not compositionally proportional. Therefore, a single dose BE study for the 20 mg strength is recommended.

In addition, regarding the clinical study discussed below, the Agency recommended that additional PK studies be conducted to support the use of an 80 mg dose from a safety perspective. These data would be useful in assessing the safety of this dose in the intended patient population in light of the potential for a higher C_{max} of the proposed drug product as compared to Prilosec.

Clinical/Statistics (Protocol OSB-IR-CO3)

"A Comparison of Omeprazole Sodium Bicarbonate – Immediate Release Powder for Suspension to Cimetidine for the Prevention of Upper Gastrointestinal Bleeding

5. Does the Agency concur with the proposed noninferiority analysis of this trial?

Agency Response:

The method of analysis appears to be acceptable.

The margin of inferiority will be a matter for review.

Discussion:

The sponsor said the margin of inferiority selected was based upon previous experience with cimetidine. The Agency does not disagree with the sponsor's proposal but cannot provide a definitive answer until the data are reviewed.

6. []

Agency Response:

[

]

Discussion:

[

]

The sponsor asked whether the proposed endpoints, based upon the pivotal studies for cimetidine, were acceptable. The Agency concurred with the proposed endpoints. The Agency would provide further comments about the study design once the protocol is submitted to the IND.

7. Does the Agency concur that Santarus may conduct a sample size recalculation at the planned interim analysis (when half the patients in the proposed sample size have completed up to 7 days of treatment), for the chosen value of delta, if the assumptions about the rates of upper GI bleeding for cimetidine and OSB-IR (PWD → require the sample size to be increased to maintain statistical power at 90%?

Agency Response:

The proposed interim analysis plan appears to be acceptable.

Discussion:

In response to the sponsor's question regarding sample size adjustment, the Agency recommended that any adjustment plan should be prospectively defined.

8. Additional Agency Recommendations (CMC):

Please provide complete CMC information for the finished drug product before Phase 3 studies begin. This information should include:

- The source and specifications for the omeprazole drug substance (reference to a DMF).
- The source and specifications for the excipients and their compendial status.
- The composition of the drug product.
- A complete description of the container/closure system.
- Stability data using that container/closure system.

We recommend you request a meeting to discuss CMC issues before or at the start of pivotal clinical trials.

Discussion:

The sponsor said complete CMC information would be submitted to the IND in a few months.

The Agency asked the sponsor to comment on whether the sodium bicarbonate component, in addition to preventing the degradation of omeprazole in an acid environment, also has an acid-neutralizing effect on patients with stress ulcer. If so, sodium bicarbonate would be considered an active ingredient and OSB-IR (PWD — ' would be considered a combination drug product (21 CFR 300.50). The sponsor explained that although gastric acid will be continuously suctioned (via nasogastric tube) during the course of the study, sodium bicarbonate is needed to prevent degradation of omeprazole. The peak plasma level of sodium bicarbonate occurs within the first 30 minutes after administration so any antacid effect would be short-lived. The Agency advised the sponsor to include in the IND a discussion justifying its position that the proposed drug product is not a combination drug product.

9. Additional Agency Recommendations (Pediatrics):

Please submit your plans for pediatric studies [21 CFR 314.55(a)].

Discussion:

The sponsor said the proposed pivotal study to be conducted in support of the new indication (prevention of upper GI bleeding in the prevention of SRMD) includes patients 16 years of age and older. Although there is a small corresponding pediatric population for this indication, it is the sponsor's position that a controlled study across all pediatric age

groups would be impossible because of the number of patients needed to demonstrate significance on the clinical endpoints. The Agency said data to assess the safety and efficacy of the proposed drug product for this indication in pediatric patients are needed. The sponsor should explore how the course of the condition and the effect of the drug in children compare to that in adults. If sufficiently similar, efficacy in pediatric patients may be extrapolated from the proposed pivotal study in adults with additional PK/PD data. The Agency recognized the difficulties in conducting studies in pediatric patients and will provide advice on study designs.

The Agency commented that the proposed drug product is a formulation that can be administered to pediatric patients of all ages and treatment of pediatric GERD represents a large clinical need. The sponsor recognized this need and said if the approved indications for Prilosec could be included in the labeling for the proposed drug product based on the proposed PK/PD study, then pediatric information would also be included. If not, however, the sponsor does not plan to pursue an indication for GERD.

The sponsor asked if pediatric data are required before submission of the NDA. The Agency would not delay the approval of an adult indication if pediatric data were not included in the NDA. However, pediatric studies should be ongoing at the time of submission of the NDA

10. Miscellaneous Issues:

The sponsor plans to submit an electronic NDA/Common Technical Document (CTD) and asked who should be contacted for advice on its plans. The Agency referenced the *Guidance for Industry: Providing Regulatory Submission in Electronic Format* and said that Dr. Randy Levin, Associate Director for Electronic Review, is the contact person for matters relating to electronic submissions.

The sponsor asked if the NDA would receive a priority review designation. The Agency said this determination would be made once the NDA is submitted. In response to the sponsor's question, the Agency said inclusion of pediatric data in the NDA would influence the decision for priority review designation.

Minutes Preparer:

Chair Concurrence:

Meeting Minutes

Page 9

Drafted: M.Walsh 12/6/01

Initialed by: S.Al-Fayoumi 12/7/01

S.Doddapaneni 12/7/01

T.Permutt 12/10/01

A.Shaw 12/10/01

L.Zhou 12/10/01

H.Gallo-Torres 12/10/01

D.Hare 12/6/01

J.Korvick 12/12/01

Final: M.Walsh 12/13/01

Filename: I46656.October1-2001.minutes.doc

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/s/

Joyce Korvick
12/20/01 05:02:42 PM