CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.5.2. PATENT CERTIFICATIONS

Paragraph IV Certification

Pursuant to §505(b)(2) of the Federal Food, Drug, and Cosmetic Act and the Food and Drug Administration regulations codified in 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 Zegerid® (omeprazole) Capsules 20 mg and 40 mg, for which the §505(b)(2) application is being 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).

Carey Fox
Vice President, Legal Affairs

4/19/05
Date

Appears This Way
On Original

1.3.5.1. PATENT INFORMATION

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

US Patent No.	Expiration Date	Type	Patent Owner
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
6,699,885	July 16, 2016	Method of Use	The Curators of the University of Missouri

The undersigned declares that the above stated United States Patent Numbers 6,489,346, 6,645,988, and 6,699,885 cover the composition and/or method of use of Zegerid® (omeprazole) Capsules 20 mg and 40 mg, which product is the subject of this application for which approval is being sought.

Joseph A. Mahoney
Patent Counsel

April 12, 2005
Date

*Insert Forms 3542a

Appears This Way
On Original

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-849

NAME OF APPLICANT / NDA HOLDER
Santarus, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
Zegerid®

ACTIVE INGREDIENT(S)
Omeprazole

STRENGTH(S)
20 mg and 40 mg

DOSAGE FORM
Capsule

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
6,489,346

b. Issue Date of Patent
12/3/2002

c. Expiration Date of Patent
7/16/2016

d. Name of Patent Owner
Curators of the University of Missouri

Address *(of Patent Owner)*
615 Locust Street, Building 304F

City/State
Columbia, MO

ZIP Code
65211

FAX Number *(if available)*
(573) 882-1130

Telephone Number
(573) 882-2821

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

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)* 24, 26, 31, 32, 34, 35, 37, 38, 49, 50, 51, 55, 56, 91, 92, 93, and 117	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: treatment of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD) and erosive esophagitis, and maintenance of healing of erosive esophagitis	

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
Joseph A. Mahoney	April 14, 2005

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, IL
ZIP Code 60603	Telephone Number (312) 701-8979
FAX Number *(if available)* (312) 706-9000	E-Mail Address *(if available)* jamahoney@mayerbrownrowe.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-849

NAME OF APPLICANT / NDA HOLDER
Santarus, Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
Zegerid®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Omeprazole	20 mg and 40 mg

DOSAGE FORM
Capsule

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	c. Expiration Date of Patent
6,645,988	11/11/2003	7/16/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
Curators of the University of Missouri	615 Locust Street, Building 304F	
	City/State: Columbia, MO	
	ZIP Code: 65211	FAX Number *(if available)*: (573) 882-1130
	Telephone Number: (573) 882-2821	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

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)*	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	

6. Declaration Certification

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

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Joseph A. Mahoney	April 14, 2005

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, IL
ZIP Code 60603	Telephone Number (312) 701-8979
FAX Number *(if available)* (312) 706-9000	E-Mail Address *(if available)* jamahoney@mayerbrownrowe.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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First Section

Complete all items in this section.

1. General Section

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1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

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1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

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Santarus, Inc.

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ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
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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	b. Issue Date of Patent	c. Expiration Date of Patent
6,699,885	3/2/2004	7/16/2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
Curators of the University of Missouri	615 Locust Street, Building 304F	
	City/State: Columbia, MO	
	ZIP Code: 65211	FAX Number *(if available)*: (573) 882-1130
	Telephone Number: (573) 882-2821	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

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)* 1-10, 13-18, 23 and 25	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: treatment of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD) and erosive esophagitis, and maintenance of healing of erosive esophagitis	

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
Joseph A. Mahoney	April 14, 2005

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, IL
ZIP Code 60603	Telephone Number (312) 701-8979
FAX Number *(if available)* (312) 706-9000	E-Mail Address *(if available)* jamahoney@mayerbrownrowe.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 21-849 SUPPL # N/A HFD # 180

Trade Name Zegerid Capsules, 20 mg and 40 mg

Generic Name omeprazole/sodium bicarbonate

Applicant Name Santarus, Inc.

Approval Date, If Known 02/27/06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

The current submission (NDA 21-849) for Zegerid 20 and 40 mg Immediate Release (IR) capsules, filed under 505(b)(2) provisions, consists of two clinical pharmacology studies, OME-IR (CAP)-C01 and OME-IR (CAP)-C02, plus supportive studies. Study OME-IR (CAP)-C01 evaluated the Pharmacokinetics (PK) and Pharmacodynamics (PD) of omeprazole when Zegerid IR 20 mg capsule was given 1 hour-premeal QD vs. Prilosec Delayed Release (DR) 20 mg capsule given QD for 7 days. Study OME-IR (CAP)-C02 evaluated similarly the PK and PD of omeprazole when Zegerid IR 40 mg capsule was given 1 hour-postmeal on Day 8 vs. Zegerid given 1 hour-premal on Day 7 for both Zegerid IR 20 and 40 mg capsules.

Based on the Agency's bioequivalence acceptance criteria for PK data obtained from Day 7, Zegerid IR 20 or 40 mg capsule is not bioequivalent (BE) to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid capsules had higher mean Cmax value of Zegerid IR 40 mg capsule obtained from this NDA was found to be comparable (3% lower) compared to the mean Cmax value obtained from Zegerid 40 mg IR powder for oral suspension which has been determined to be safe based on a previous clinical safety study.

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:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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?

Pediatric exclusivity was granted prior to the submission of this application and is not related to it.

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

NDA# 19-810 Prilosec (omeprazole) Delayed-Release Capsules

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 NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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 ☐

Investigation #2 YES ☐ NO ☐

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

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"):

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 # YES ☐ ! NO ☐

! Explain:

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Mary M. Lewis
Title: Regulatory Project Manager
Date: 2/3/06 and 3/30/06

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.
Title: Deputy Division Director
Division of Gastroenterology Products

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

1.3.5.3 STATEMENT OF CLAIMED EXCLUSIVITY

Santarus, Inc. is not claiming any marketing exclusivity under the provisions of 21 CFR §314.108.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : NDA 21-849 **Supplement Type (e.g. SE5): _____** **Supplement Number:**

Stamp Date: 4/27/05 **Action Date: 2/26/06**

HFD 180 **Trade and generic names/dosage form: Zegerid (omeprazole) Capsule; 20 mg, 40 mg**

Applicant: Santarus, Inc. **Therapeutic Class: 4 ↓ 3**

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 5

Indication #1: 20 mg: short-term treatment of active duodenal ulcer.

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-849
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: 20mg: treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD)

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-849
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

Indication #3: 20 mg: Short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

Is there a full waiver for this indication (check one)?

☒X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒X Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

Indication #4: 20 mg: Maintenance of healing of erosive esophagitis (EE).

Is there a full waiver for this indication (check one)?

☒X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒X Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

Indication #5: 40 mg: Short-term treatment (4-8 weeks) of active benign gastric ulcer.

Is there a full waiver for this indication (check one)?

☒X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☒ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

1.9.2 REQUEST FOR WAIVER OF PEDIATRIC STUDIES

In accordance with 21 CFR §314.55(c) the sponsor hereby requests a waiver of the requirements for assessment of the safety and effectiveness of ZEGERID® Capsules in pediatric patients. The rationale of the waiver request is discussed below. The waiver request contains the information and discussion recommended in Appendix A of the Agency's Guidance Document entitled, "Guidance for Industry - Recommendations for Complying with the Pediatric Rule [21 CFR 314.55(a)]" (issued November 2000).

NDA Number:	21-849
Product:	ZEGERID® (omeprazole) Capsules 20 mg and 40 mg
Sponsor:	Santarus, Inc. 10590 West Ocean Air Dr., Suite 200 San Diego, CA 92130
Indications:	**Duodenal Ulcer.** ZEGERID® is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. **Gastric Ulcer.** ZEGERID® is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. **Treatment of Gastroesophageal Reflux Disease (GERD)** *Symptomatic GERD.* ZEGERID® Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD. *Erosive Esophagitis.* ZEGERID® Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. The efficacy of ZEGERID® used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered. **Maintenance of Healing of Erosive Esophagitis.** ZEGERID® Capsules are indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.
Age ranges included in waiver request:	All Pediatric Age Groups
Reasons for waiving pediatric studies:	(a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients.

Justification for waiver:	In accordance with 21 CFR §314.55(c), the sponsor requests a full waiver from the requirement that the new drug application contain data on the assessment of safety and effectiveness of ZEGERID® Capsules for the claimed indications in pediatric patients. The sponsor believes that a waiver of the requirement to conduct clinical studies in pediatric patients is justified by virtue of the following: 1. The physical size of the capsule dosage form. The composition of the ZEGERID® Capsule formulation requires a capsule shell of —size; the dimensions of — capsules are summarized below: External Diameter, Body: — mm External Diameter, Cap: — mm Overall Closed Length: — mm The 00 size capsule is the smallest size that will accommodate the ZEGERID formulation, but a — size capsule is not an appropriate dosage form for pediatric patients, especially for pediatric patients < 12 years of age. It is unlikely that a capsule of this size will be easily swallowed - resulting in low patient compliance. Because of the capsule size, it is unlikely to be used in pediatric patients. Moreover, the availability of dosage form suitable for administration to children, namely ZEGERID® Powder for Oral Suspension, makes it unnecessary for the 00 size capsules to be prescribed for pediatric patients < 12 years. 2. The sponsor also believes a waiver is justified because the course of the disease (acid-related gastrointestinal disease, including symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis) and the effects of the drug are so similar in adults and pediatric patients ≥ 12 years that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults. In fact, current labeling for Prilosec® (omeprazole) Capsules indicates that a dose of 20 mg is appropriate for children age 2 years and above with body weight at least 20 kg. Assessments of safety and effectiveness of ZEGERID® Capsules in pediatric patients would be very unlikely to reveal any meaningful therapeutic benefit over the existing dosage forms appropriate for pediatric patients.

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.

Christine Simmons

April 12, 2005

Christine Simmons, PharmD
Vice President, Regulatory Affairs and Quality Assurance

Date

Appears This Way
On Original

NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

NDA 21-849	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zegerid (omeprazole/sodium bicarbonate) Capsules 20 mg & 40 mg		Applicant: Santarus, Inc.	
RPM: Mary M. Lewis		HFD-180	Phone # 301-796-0941
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-810 Prilosec® (omeprazole) Delayed-Release Capsules	
❖ Application Classifications:			
• Review priority		(X) Standard ( ) Priority	
• Chem class (NDAs only)		3 → 4 pmt	
• Other (e.g., orphan, OTC)		N/A	
❖ User Fee Goal Dates		**February 26, 2006**	

Reviewers Sign Off List

Moo-Jhong Rhee, Ph.D., Chief, Branch III ~~Hasmukh Patel, Ph.D., Chemistry Team Leader~~ 2/7/06

Ruyi He, M.D., Medical Team Leader 2/3/06

E. Dennis Bashaw,Pharm.D., Biopharmaceutics Team Leader 2/6/06

Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist 2/3/06.

Brian Strongin, Chief, Project Management Staff _____signed off 2/2/06.

Joyce Korvick, M.D., M.P.H. Deputy Division Director 2/23/06

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-849	Efficacy Supplement Type - N/A	Supplement Number N/A	
Drug: ZEGERID (omeprazole/sodium bicarbonate) Capsules		Applicant: Santarus, Inc.	
RPM: Mary M. Lewis		HFD-180	Phone # 301-796-0941
Application Type: () 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-810 Prilosec® Delayed-Release Capsules	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3 and 4
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	02/26/2006
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	() Paid
• User Fee waiver	(X) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ 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.	(X) Verified () N/A
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III (X) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• 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).	(X) Verified () N/A
❖ Exclusivity Summary (approvals only)	X

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	01/25/06
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	01/27/06
• Most recent applicant-proposed labeling	01/04/06
• Original applicant-proposed labeling	04/26/05
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 01/25/06 DMETS 08/25/05 DDMAC 01/17/06; M.O. 01/19/06; CMC 12/9/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Prilosec, Prevacid, Nexium, Protonix, Aciphex
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	04/26/05
• Reviews	DMETS 08/25/05, 01/25/06; DDMAC 01/17/06
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes, 1
• Documentation of discussions and/or agreements relating to post-marketing commitments	Sponsor 2/23/06; AP letter 2/27/06
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	10/22/04
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• 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

Clinical/Statistical Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	2/17/06
❖ Clinical review(s) *(indicate date for each review)*	01/19/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X; Sponsor requested a waiver.
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	7/18/05, 2/1/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	01/06/06, 1 more pending.
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	12/09/05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	12/09/05 (page 68 CMC)
• 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)	Date completed: 6/10/05 **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X) N/A** ( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**01/31/06** **Ref: IND 69,937; 06/10/05**
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

MML 2/3/06, and 3/30/06.

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

/s/

Mary Lewis
3/30/2006 03:38:21 PM

Mary Lewis
3/30/2006 03:38:21 PM

Lewis, Mary

From: CDER DocAdmin, DFS
Sent: Thursday, March 02, 2006 3:22 PM
To: Lewis, Mary; Peat, Raquel
Subject: DFS Email - N 021849 N 000 26-Apr-2005 - Review


090014648060d333 .drl (184 B)
090014648060d333 .pdf (32 KB)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 021849 N 000 26-Apr-2005	X83	02-Mar-2006	CM

Document Type: Review
Submission Description: Appen B Amendment 2 022706
PM activity: PM activity required

Author(s)/Discipline(s)

1. Mary Lewis, CSO

Signer(s)

1. Mary Lewis
   02-Mar-2006
2. Mary Lewis
   02-Mar-2006

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NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 21-849 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Zegerid Capsules
Established Name: omeprazole
Strengths: 20 and 40 mg

Applicant: Santarus, Inc.
Agent for Applicant: N/A

Date of Application: April 26, 205
Date of Receipt: April 27, 2005
Date clock started after UN: N/A
Date of Filing Meeting: June 10, 2005
Filing Date: June 26, 2005
Action Goal Date (optional): User Fee Goal Date: February 26, 2006

Indication(s) requested: For short-term treatment of active duodenal ulcer; short-term treatment of active benign gastric ulcer; treatment of heartburn and other symptoms associated with GERD; short-term treatment of erosive esophagitis; and for maintenance of healing of erosive esophagitis.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
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 ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ 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 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 ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- 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 ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All except the forms listed below.

Additional comments: The following forms were submitted in paper: forms 356h; 3397; Field Copy Certification; Debarment Certification; Financial interests and arrangements of clinical investigators certification; Patent Information, form 3542a; and Patent Certifications.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? 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? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 69,937

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 10/22/04 CMC Meeting NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/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? YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ 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? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 10, 2005

BACKGROUND: This application was submitted in Common Technical Document format. This is a non-fee paying 505(b)(2) application. Santarus, Inc. is the sponsor for NDA 21-636 Zegerid (omeprazole) Oral Powder for Suspension, 20 mg and was approved on June 15, 2004. NDA 21-636 indications are for: : short-term treatment of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment of erosive esophagitis; and maintenance of healing of erosive esophagitis. Santarus, Inc. is also the sponsor of NDA 21-706 for Zegerid (omeprazole) Oral Powder for Suspension, 40 mg and was approved on December 21,2004. NDA 21-706 indications are for: short-term treatment of active benign gastric ulcer, and prevention of upper gastrointestinal bleeding in critically ill patients.

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

ATTENDEES:
Joyce Korvick, M.D., Deputy Division Director
Ruyi He, M.D., Medical Officer Team Leader
Lolita Lopez, M.D., Medical Reviewer
Maria Ysern, M.S., Chemistry Reviewer
Sushanta Chakder, Ph.D., Pharmacology Reviewer
Jasti Choudary, B.V.Sc., Ph.D., Pharmacology Team Leader
Tien-Mien Chen,Ph.D., Biopharmacology Reviewer
Brian Strongin, R.Ph., M.B.A., Chief, Project Management Staff
Mary M. Lewis, BSN, Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Lolita Lopez
Secondary Medical:	Ruyi He
Statistical:	(Stella Grosser)
Pharmacology:	Sushanta Chakder
Statistical Pharmacology:	N/A
Chemistry:	Maria Ysern
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Tien-Mien Chen
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	C.T. Viswanathan, Ph.D.
Regulatory Project Management:	Mary Lewis
Other Consults:	DDMAC: Shannon Benedetto; DMETS:

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 _____ 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? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☒ NO ☐

PHARMACOLOGY N/A ☐ 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: In our Filing Letter we requested: A summary of post-marketing safety information for Zegerid suspension.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ 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 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.☒ Convey document filing issues/no filing issues to applicant by Day 74.

No filing issues.

Mary M. Lewis
Regulatory Project Manager, HFD-180

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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).

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

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☒

   *If "**No**," skip to question 3.*

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

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 ☒ NO ☐

   (***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? YES ☒ 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)? YES ☒ 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 formulation and new manufacturer.

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 ☐ NO ☒

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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

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 ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ 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)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

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

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): 4,853,230; 4,786,505; 6,147,103;6,150,380;6,166,213; 6,191,148.

NOTE: *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)
Patent number(s):

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

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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?

  YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☒ 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 ☐ NO ☒

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).

  YES ☒ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ 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?

YES ☒ NO ☐

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

/s/

Mary Lewis
7/15/05 04:13:35 PM
CSO

Mary Lewis
7/15/05 04:19:59 PM
CSO

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On Original

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

NDA 21-849
February 27, 2006
Zegerid (omeprazole/sodium bicarbonate) Capsules, 20mg/1100mg and 40mg/1100mg
Amendment 2, specifically to amend questions 3 and 4 since previous Amendment of 2/8/06.

1. Does the application reference a listed drug (approved drug)? YES ☒ 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 ☐ NO ☒

   Prilosec is a capsule as is NDA 21-849. They both have identical ingredients of omeprazole.

   (***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? YES ☒ NO ☐

   A pharmaceutical alternative is NDA 21-636 Zegerid (omeprazole) Powder for oral suspension, approved but not listed as a referenced alternative; Prilosec, OTC, NDA 21-229, approved but not listed; and NDA 19-810 approved and listed.

   (***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)? YES ☒ 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 formulation and new manufacturer.

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 ☐ NO ☒

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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

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 ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ 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)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

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

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s): 4,853,230; 4,786,505; 6,147,103; 6,150,380; 6,166,213; 6,191,148.

NOTE: *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)
Patent number(s):

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

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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?

YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☒ 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 ☐ NO ☒

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).

      YES ☒ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ 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?

    YES ☒ NO ☐

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/s/

Mary Lewis
3/2/2006 03:17:38 PM
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Mary Lewis
3/2/2006 03:21:20 PM
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Lewis, Mary

Hi Mary,

The attached files contains our written agreement to conduct the requested post marketing study on dissolution for Zegerid Capsules. One file is pdf and the other is a WORD document if you need to copy anything.

As you requested we have proposed specific dates for: Protocol Submitted, Study Start, and Final Report. I also included a commitment for Data Collection during a period covering 6 months of production. We have submitted the official version by Federal Express and we have also sent you a facsimile.

If there are questions please don't hesitate to call.

Regards,

Charley Davis

Charles H. Davis
Senior Director, Regulatory Affairs
Santarus, Inc.
10590 West Ocean Air Dr., Suite 200
San Diego, CA 92130
Office: 858-314-5753
Mobile: 949-683-0805
cdavis@santarus.com

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Lewis, Mary

From: CDER DocAdmin, DFS
Sent: Monday, February 27, 2006 3:27 PM
To: Lewis, Mary; Harvey, Brian; He, Ruyi; Lopez, Lolita
Subject: DFS Email - N 021849 N 000 26-Apr-2005 - Review

Follow Up Flag: Follow up
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090014648060a325 .drl (184 B)
090014648060a325 .pdf (91 KB)

Document room close out the following assignments:

	Personnel Code	Sup-Concur	St
N 021849 N 000 26-Apr-2005	89T	27-Feb-2006	CM

Document Type: Review
Submission Description: dep div dir approval memo
PM activity: PM activity required

Author(s)/Discipline(s)

1. Joyce Korvick, MEDICAL OFFICER

Signer(s)

1. Joyce Korvick
   27-Feb-2006

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Lewis, Mary

From: CDER DocAdmin, DFS
Sent: Monday, February 27, 2006 4:16 PM
To: Rice, Crystal; Parker, Christine S; Clarke, Patrick; Brubaker, Heidi; Castle Jr, Roy V; Doyle, Carol; Jenkins, John K; Carmouze, Grace N; Avant, Debbie; Dobbs, Maria L; Holmes, Joanne M; Jones, Michael D; Collier, Bronwyn E; Lewis, Mary; Lopez, Lolita; Ysern, Maria E; Chakder, Sushanta K; Chen, Tien Mien; Hummel, Robert; Bashaw, Edward D; Korvick, Joyce A; Harvey, Brian; Strongin, Brian K; Furness, Melissa
Subject: DFS Email - N 021849 N 000 26-Apr-2005 - NDA Letters

090014648060a3d9.drl (184 B) 090014648060a3d9.pdf (257 KB)

Document room update the following:

	Decision Date	Decision Code
N 021849 N 000 26-Apr-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BM 07-Jul-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 4P 15-Jul-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BB 10-Aug-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 SU 23-Aug-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BC 01-Nov-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BL 21-Nov-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BB 08-Dec-2005	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BL 04-Jan-2006	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BL 30-Jan-2006	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BL 10-Feb-2006	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BL 16-Feb-2006	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)
N 021849 N 000 BC 23-Feb-2006	27-Feb-2006	AP:APPROVAL (with Post Marketing Commitments)

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Document Type: NDA Letters
Letter Group: Approval Letters
Letter Name: Approval letter based on enclosed/submitted labeling text
Submission Description: AP letter 022606 w PMC and Label

Author(s)/Discipline(s)

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1. Mary Lewis, CSO

Signer(s)

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1. Mary Lewis
   Signing for Dr. Brian E. Harvey
   27-Feb-2006
2. Joyce Korvick
   for Dr. Brian E Harvey
   27-Feb-2006

Supervisory Signer(s)

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1. Joyce Korvick
   for Dr. Brian E Harvey
   27-Feb-2006

M E M O R A N D U M

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

DATE: February 24, 2006
FROM: Maria Elena Ysern, MSc, Review Chemist

THROUGH: Moo Jhong Rhee, PhD. Chief, Branch III, Pre-Marketing Assessment II

SUBJECT: Agreement of the company to Phase to commitment. Amendment 0014 dated Feb 23, 2006.

TO: NDA 21-849 Zegerid®(omeprazole/sodium bicarbonate) Capsules 20 mg/ 100mg and 40 mg/1100 mg.

This memorandum is an addendum to Chemistry Review #2.

Santarus, Inc has provide an Amendment 0014 to NDA 21-849 where they agree to perform a study consisting of expanded dissolution testing using the USP Apparatus 2 (paddle) at 75 rpm, incorporating both 30 and 45 minutes sampling time points, for a period of six months after approval, according to the following study schedule:

Protocol Submission: No later than March 31, 2006.
Study start: No later than May 1, 2006
Data Collection All lots of Zegerid Capsules (20 and 40 mg) manufactured from May 1, 2006 through October 31, 2006 (Six months of production).
Final Report Submission: No later than December 31, 2006

They understand that the Agency will re-evaluate the performance of the dissolution method, with regards to both time point and Q value based on the results of the study.
While the study is under way, Santarus will use the 45 minute data as a release specification for both Zegerid Capsules 20 mg and 40 mg with a Q value of ———————— which is the same as the currently proposed in the NDA..

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/s/

Maria Ysern
2/24/2006 03:46:29 PM
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Moo-Jhong Rhee
2/24/2006 03:49:59 PM
CHEMIST
Chief, Branch III

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2006

To: Christine Miller	**From:** Mary Lewis
Company: Santarus, Inc.	Division of Gastroenterology Products
Fax number: (858) 314-5788	**Fax number:** 301-796-9905
Phone number: (858) 314-5731	**Phone number:** 301-796-0941

Subject: Post Marketing Commitment for dissolution testing for NDA 21-849.
Please commit to the following Post Marketing Commitment.

Total no. of pages including cover: 3

Comments: Given the almost total dissolution of the product at 45 minutes, the Agency is not convinced that the proposed dissolution specification of Q= ——— minutes provides a sufficient level of quality assurance.

Please commit to perform a study consisting of expanded dissolution testing using the USP Apparatus 2 (paddle) at 75 rpm, incorporating both a 30 and 45 minute sampling timepoints, for a period of six months after approval. During this time, the 45 minute data will be used as the release specification with a Q value of ——— ———. At the end of this time, the Agency will re-evaluate the performance of the dissolution method, with regards to both timepoint and Q value based on the results of these production lots.

Document to be mailed: ☑ YES ☐ NO

Attachment

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/s/

Mary Lewis
2/23/2006 02:19:24 PM
CSO

Mary Lewis
2/23/2006 02:23:08 PM
CSO

Lewis, Mary

From: Charley Davis [CDavis@santarus.com]
Sent: Thursday, February 23, 2006 4:11 PM
To: Lewis, Mary
Subject: NDA 21-849 Zegerid Capsules Post Marketing Commitment

Follow Up Flag: Follow up
Flag Status: Flagged


Untitled Attachment


NDA 21-849 Post Marketing Comm...


NDA 21-849 Dissolution Specifi...

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SANTARUS, INC.®

10590 WEST OCEAN AIR DRIVE, SUITE 200
SAN DIEGO, CALIFORNIA 92130
858.314.5700 ▼ FAX 858.314.5701
www.santarus.com

February 23, 2006

Brian Harvey, MD, PhD
Director, Division of Gastroenterology Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-849
ZEGERID® (omeprazole/sodium bicarbonate) Capsules 20 mg/1100 mg and 40 mg/1100 mg
Amendment 0014
Response to FDA Fax Dated February 23, 2006

Dear Dr. Harvey:

Reference is made to NDA 21-849 for Zegerid (omeprazole/sodium bicarbonate) Capsules 20 mg/1100 mg and 40 mg/1100 mg originally submitted on April 26, 2005. Reference is also made to the facsimile communication received on February 23, 2006 which requested a commitment to perform a study of expanded dissolution testing.

Santarus here agrees to perform a study consisting of expanded dissolution testing using the USP Apparatus 2 (paddle) at 75 rpm, incorporating both 30 and 45 minute sampling time points, for a period of six months after approval, according to the following study schedule:

Protocol Submission	Not later than March 31, 2006
Study Start	Not later than May 1, 2006
Data collection	All lots of Zegerid Capsules (20 mg and 40 mg) manufactured from May 1, 2006 through October 31, 2006 (Six months of production)
Final Report Submission	Not later than December 31, 2006

We understand that the Agency will re-evaluate the performance of the dissolution method, with regards to both time point and Q value based on the results of study.

During the time that the study is underway Santarus will use the 45 minute data as the release specification for both Zegerid Capsules 20 mg and 40 mg with a Q value of ——————— ————). The acceptance criteria will be the same as currently proposed in the NDA (ie, conformance to USP <711> requirements).

If you should have any questions regarding the information submitted, please contact Mr. Charles Davis, Senior Director, Regulatory Affairs for Santarus at telephone number: 858-314-5753, facsimile number: 858-314-5788 or e-mail: cdavis@santarus.com.

Sincerely,

Charles H. Davis, RAC
Senior Director, Regulatory Affairs

Virus-free Statement: This submission is virus free. The CD-ROM was scanned using Trend Micro OfficeScan Client for Windows XP/2000/NT, Program Version 6.0, VSApiNT Version 8.000.1001, TmFilter Version 8.000.0.1001, Virus Pattern File Number 3.229.00 (Trend Micro Inc). Additionally, our system is automatically updated with the latest virus definition patterns in order to ensure the best protection against viruses.

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 22, 2006

To: Christine Miller	**From:** Melissa Furness for Mary Lewis
Company: Santarus, Inc.	Division of Gastroenterology Products
Fax number: (858) 314-5788	**Fax number:** 301-796-9905
Phone number: (858) 314-5731	**Phone number:** 301-796-0893

Subject: Dissolution Specifications for NDA 21-849

Total no. of pages including cover: 3

Comments: Please commit to the following as soon as possible (via mail and fax): "The following dissolution specifications should be implemented: Q= ~ at ———— for both Zegerid Immediate Release Capsules 20 and 40 mg."

Document to be mailed: ☐ YES ☑ NO

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/s/

Mary Lewis
2/22/2006 11:37:45 AM
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MEMORANDUM

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

DATE: 2/17/06

FROM: Joyce A Korvick, MD, MPH

DGP/ODE III

SUBJECT: Deputy Division Director Approval Comments
NDA 21-849

APPLICANT: Santarus, Inc.

DRUG: **Zegerid® (omeprazole/sodium bicarbonate)**
20 mg omeprazole/1100 mg of sodium bicarbonate or
40 mg omeprazole/1100 mg of sodium bicarbonate capsules

DIVISION RECOMMENDATION:
The review team recommends an approval action for the current application. I agree with this recommendation:

Zegerid 20 mg Capsules:

- short-term treatment of 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
- maintenance of healing of erosive esophagitis (EE)

Zegerid 40 mg Capsules:

- short-term treatment (4-8 weeks) of active benign gastric ulcer.

No Risk Management steps are needed.

Phase 4 commitment:
A study consisting of expanded dissolution testing using the USP Apparatus 2(paddle) at 75 rpm, incorporating both 30 and 45 minute sampling time points, for all lots manufactured during the first six months after approval, according to the following study schedule:

Protocol Submission: by March 31, 2006
Study Start Date: by May 1, 2006
Final Report Submission: by December 31, 2006.

Pediatric Recommendations:
The sponsor is requesting a waiver for pediatric studies; I recommend that this request be granted. The reference listed drug, Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Zegerid capsule will not offer meaningful therapeutic benefit over existing delayed release omeprazole formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce). Finally, the dosing of sodium bicarbonate may be an safety issue for younger children.

Regulatory History of Zegerid formulations:

NDA 21636
Original approval June, 2004
Zegerid® (omeprazole/sodium bicarbonate) Powder for Oral Suspension, 20 mg sodium bicarbonate 1680 mg sodium bicarbonate

This was a 505(b)(2) application of a new formulation of the omeprazole product based upon the approved prescription omeprazole product (Prilosec). The firm is referencing the Agency's findings of safety and efficacy for clinical and non-clinical studies from NDA 19-810 for Prilosec (Omeprazole) Delayed-Release Capsules. This product is an immediate release powder for oral suspension in water. The product includes sodium bicarbonate, which helps to prevent the degradation of the omeprazole powder by the gastric acid. The sodium bicarbonate, at the appropriate dose, is not intended to treat the medical conditions for which this product is being approved, but rather to enhance the efficacy of immediate release omeprazole. The applicant included chemistry and manufacturing information as well as clinical pharmacology studies in this application.

Approved indications:
1. Short-term treatment of active duodenal ulcer.
2. Treatment of Gastroesophageal Reflux Disease (GERD)
    a. Symptomatic GERD
    b. Erosive Esophagitis
3. Maintenance of Healing of Erosive Esophagitis

NDA 21-706
Zegerid® (omeprazole/sodium bicarbonate) Powder for Oral Suspension,
40 mg sodium bicarbonate 1680 mg sodium bicarbonate
Action Date: December 2006

Approved indications:
"ZEGERID™ Powder for Oral Suspension is indicated for short term treatment (4 to 8 weeks) of active benign gastric ulcer."

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

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 prevention of upper GI bleeding in critically ill patients. The first indication is an approved indication for the reference drug, omeprazole delayed-release, and Zegerid 40 mg Powder for Oral Suspension relies on the efficacy finding of the Agency under 505 (b)(2). The approval action for the second indication relied upon new clinical trials data submitted by the sponsor.

Zegerid Powder for Oral Suspension, unlike the previously approved delayed release formulations of omeprazole that have an enteric-coating which provides protection from rapid degradation upon exposure to gastric acid, contains 20 mEq sodium bicarbonate that replaces the enteric coating. The primary role of the sodium bicarbonate is to neutralize gastric acid and protect omeprazole from gastric acid degradation until it can be absorbed. Both 20 and 40 mg Zegerid (omeprazole/sodium bicarbonate) Powder for Oral suspension products were submitted as a 505(b)(2) application and relied on the Agency's finding of safety and efficacy of omeprazole. The reference listed drug (RLD) was Prilosec® Delayed Release Capsule.

NDA 21-849
Current Application for capsule formulation:

Zegerid® (omeprazole/sodium bicarbonate)
20 mg omeprazole/1100 mg of sodium bicarbonate or
40 mg omeprazole/1100 mg of sodium bicarbonate capsules

The sponsor submitted this NDA as a 505(b)(2) application using Prilosec® Delayed Capsules as the RLD and relies on the Agency's previous finding of safety and effectiveness for omeprazole. The sponsor conducted two bioequivalent studies comparing the PK and PD of Zegerid Capsules and Prilosec® Delayed-Release Capsules at dosage strengths of 20 mg and 40 mg of omeprazole in healthy adult subjects. Similar to the Zegerid Powder for Oral Suspension, the enteric coating is replaced by 13 mEq (1100 mg) sodium bicarbonate. No claim is being made by the sponsor regarding the therapeutic effect of sodium bicarbonate.

Clinical Pharmacokinetics of the capsule formulations:
When comparing an immediate-release to a delayed release formulation, the peak plasma omeprazole concentration (Cmax) for Zegerid® Capsules was higher than the Cmax for Prilosec with both the 20-mg and 40-mg doses. However, the mean Cmax for Zegerid® Capsules 20 mg (679.8 ng/mL) is lower than the mean Cmax for Prilosec 40 mg (1344 ng/mL) and the Zegerid® Capsule 40-mg Cmax (1526 ng/mL) was within the steady-state exposure envelope for the marketed formulation of Zegerid® Powder for Oral Suspension 40 mg (1954 ng/mL). Therefore, there should be no new or unexpected safety issues associated with the Cmax for Zegerid® Capsules 20 and 40 mg; the labeling for Prilosec and for Zegerid® Powder for Oral Suspension should appropriately describe the safety profile for Zegerid® Capsules. The omeprazole pharmacokinetics and pharmacdynamics of this formulation are similar to Zegrid® Powder for Oral Suspension; therefore, the small difference in the sodium bicarbonate content does not result in a clinically meaningful difference in efficacy.

The safety of Zegerid® Capsules 20 mg and 40 mg is also supported by data from Santarus PK/PD trials with data from Zegerid® Powder for Oral Suspension trials comparing the PK and PD profiles of Zegerid® and Prilosec, 20 mg and 40 mg doses, respectively, in healthy adults. The duration of exposure to Zegerid® Oral Suspension in these trials was ≤ 8 days. Almost all the AEs reported in these trials were rated as mild with no severe AEs nor deaths reported. An additional 8-week open label safety trial, OME-IR (SUSP)-C07 was also conducted (225 patients completed) with gastric acid related diseases using with Zegerid® Oral Suspension 40 mg. The Zegerid® safety data from this trial are similar to the safety data for Prilosec. See reviews of NDAs 21-636 and 21-706.

Zegerid capsules contain sodium (—— mg) in the form of sodium bicarbonate; therefore, it should be taken with caution in patients on sodium restricted diet. This formulation also contains 1100 (13meq) of sodium bicarbonate; sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. It should also be used with caution in patients Bartter's syndrome, hypokalemia, respiratory alkalosis and those with problems with systemic acid-base balance. Further, long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome. Known adverse reactions (rate unknown) with sodium bicarbonate include: abdominal pain, flatulence, hypernatremia, metabolic alkalosis, peripheral edema, seizures, tetany, and tremor.

There is a similar food effect as that seen with the Zegerid Powder for Oral Suspension, and a recommendation for administration of the Zegerid Capsule 1 hour prior to meals as it is currently labeled for the Oral Suspension.

From the view point of Office of Clinical Pharmacology and Biopharmaceutics (OCPB), NDA 21-849 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to the labeling (see below).

Given the almost total dissolution of the product at 45 minutes, the Agency is not convinced that the proposed dissolution specification of Q=' ——— provides a sufficient level of quality assurance. The sponsor should commit to performing expanded dissolution testing using the USP Apparatus 2 (paddle) at 75 rpm, incorporating both a 30 and 45min sampling time points, within a period of six months after approval. During this time the 45min data will be used as the release specification with a Q value of —— ——————. At the end of this time the Agency will re-evaluate the performance of the dissolution method, with regards to both time point and Q value based on the results of these production lots. Santarus has agreed to this and it will be placed in the action letter as a phase 4 commitment.

Pre-Clinical:
There are no outstanding concerns for pre-clinical toxicology and pharmacolgy.

CMC:
There are no outstanding CMC issues.

Combination drug products:
How did this product met 21 CFR 300.50?
The division feels that the sponsor addressed the combination issue under 21 CFR 300.50 (a)(1) "Special cases of this general rule are where a component is added to enhance the safety or effectiveness of the principal active component." This was addressed in the original application (NDA #21636), although not designated as such at that time. In this case Santarus supplied evidence that omeprazole (immediate release) would not be effective for the approved indication (Gastroesophageal Reflux Disease) if it was not somehow protected from the acidic environment of the stomach. The innovator achieves this by enteric coating the omeprazole, thus preventing acid degradation of omeprazole. In the case of Zegerid, the protection is afforded by a dose of sodium bicarbonate. Omeprazole is approved for a single daily dose. As such it is expected to treat GERD including the maintenance and healing of erosive esophagitis. Sodium bicarbonate at the quantity present in the combination product is effective in raising the gastric pH for approximately 1 hour. The etiology of reflux disease is such that healing is promoted with sustained acid suppression over a substantial portion of a 24 hour period and for several weeks (up to 8 weeks). Thus, while patients might experience a short period of "heart burn" relief due to the sodium bicarbonate, sodium bicarbonate taken in this dose once per day is not an effective treatment for GERD and erosive esophagitis. The sponsor claims that it is added to prevent degradation of the immediate release omeprazole. The sponsor demonstrated this in the pharmacokinetic and pharmacodynamic studies that they supplied in the NDA. Thus, the studies submitted by Santarus were sufficient to address the combination product issue.

PK/PD studies:
Santarus submitted 3 clinical pharmacology studies to this NDA 21,636. Two study the pharmacokinetic and pharmacodynamic profiles of the 40-mg dose. One study, OSB-IRC06 studies the 20-mg dose. In this study the comparison of the PK profiles following administration of multiple 20 mg doses of omeprazole powder and Prilosec Delayed Release Capsules indicated that the Cmax for omeprazole power 20mg was higher

(57- 60%) than that for the Delayed-Release product. Thus, the two preparations are not bioequivalent; however, the AUCs are similar. The pharmacodynamic results reveal similar profiles for intragastric pH between the two formulations for integrated acidity, mean gastric acid concentration; percent time gastric pH < 4, and mean gastric pH. Control arms in these studies included immediate release omeprazole without bicarbonate. There were no bicarbonate alone arms. The studies demonstrated that the PK/PD of immediate release omeprazole was similar to that of placebo, and thus would not be effective in treating GERD.

This profile was adequate to address the efficacy of omeprazole "immediate release" formulation and the protective activity of sodium bicarbonate in this new formulation. The data also shows that if the sodium bicarbonate was not present the omeprazole would be degraded and thus there would be no efficacy for GERD. Thus, this component "enhances" the activity of the immediate release omeprazole. No additional clinical trials were requested by the division.

Nomenclature:
The fact that the established name appears in Santarus' proposed labeling as (omeprazole) does not address the combination status, and thus will be amended to (omeprazole/sodium bicarbonate), in order to reflect this labeling change (see below). Thus, the label will acknowledge the fact that there are two active components of this drug, the omeprazole being the active moiety, effective for the approved indications.

LABELING:
The proposed label includes both the oral suspension formulation as well as the capsule formulation.

The label relies on the findings of efficacy from the reference listed drug which does not contain sodium bicarbonate. It was important in construction of these labels to emphasize the concentration of sodium bicarbonate as well as the fact that while each formulation had the same amount of sodium bicarbonate regardless of the dose of omeprazole two 20 mg strength formulations did not equal a 40 mg dose since they would have twice as much sodium bicarbonate as the approved 40 mg dose.

Finally, the review team did conclude that the 40 mg powder formulation was interchangeable with the 40 mg Capsule with regard to efficacy of omeprazole. There was a slightly different concentration of sodium bicarbonate, which for the healthy patient was not a clinically significant difference. The same is true for the 20 mg Power for Oral Suspension and Capsules. There are statements in the label regarding the use of these sodium containing preparations in patients with renal insufficiency.

Finally the established name has been changed to reflect the active ingredient sodium bicarbonate (see below).

Proposed Labeling:

ZEGERID®
(omeprazole/sodium bicarbonate)

ZEGERID is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and magnesium stearate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

The label uses this terminology throughout to emphasize that these formulations contain sodium bicarbonate: e.g. **ZEGERID Oral Suspension 40 mg/1680 mg.**

CLINICAL PHARMACOLOGY
Omeprazole is acid labile and thus rapidly degraded by gastric acid. ZEGERID Capsules and Powder for Oral Suspension are immediate release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

Pharmacokinetics:

Absorption
In separate in vivo bioavailability studies, when ZEGERID Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10 90 min) after a single dose or repeated dose administration. Absolute bioavailability of ZEGERID Powder for Oral Suspension (compared to I.V. administration) is about 30 40% at doses of 20 – 40 mg, due in large part to presystemic metabolism.

When ZEGERID Oral Suspension 40 mg/1680 mg was administered in a two dose loading regimen, the omeprazole AUC(0 inf) (nghr/mL) was 1665 after Dose 1 and 3356 after Dose 2, while Tmax was approximately 30 minutes for both Dose 1 and Dose 2. Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from ZEGERID are approximately proportional from 20 to 40 mg doses, but a greater than linear mean AUC (three fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole from ZEGERID increases upon repeated administration.

When ZEGERID is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% relative to administration 1 hour prior to a meal.

(see approval letter for final package insert)

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/s/

Joyce Korvick
2/27/2006 03:26:51 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 10, 2006

To: Charles Davis	**From:** Mary Lewis
Company: Santarus, Inc.	Division of Gastroenterology Products
Fax number: (858) 314-5788	**Fax number:**
Phone number: (858) 314-5753	**Phone number:** 301-796-0941

Subject: Additional language for the Dosage and Administration section of the label.

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☑ YES ☐ NO

Attachment

2/10/06 In response to our teleconference today.

Additional Recommendations to the Zegerid label (NDA 21-849) similar to the Augmentin label:

Under DOSAGE AND ADMINISTRATION section, first sentence:

Recommend:

Since both the 20 mg and 40 mg **oral suspension** packets contain the same amount of sodium bicarbonate (1680 mg), two packets of 20 mg are not equivalent to one packet of Zegerid 40 mg; therefore, two 20 mg packets of Zegerid should not be substituted for one packet of Zegerid 40 mg.

Since both the 20 mg and 40 mg **capsules** contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are not equivalent to one capsule of Zegerid 40 mg; therefore, two 20 mg capsules of Zegerid should not be substituted for one capsule of Zegerid 40 mg.

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

/s/

Mary Lewis
2/10/2006 02:33:15 PM
CSO

Mary Lewis
2/10/2006 02:37:15 PM
CSO

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SANTARUS, INC.®

10590 W. OCEAN AIR DRIVE, SUITE 200
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858.314.5700 ▼ FAX 858.314.5701
www.santarus.com

January 30, 2006

Brian Harvey, MD, PhD
Director, Division of Gastroenterology Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-849
Zegerid® (omeprazole) Capsules 20 mg and 40 mg
Amendment 0010
Response to January 27, 2006 Fax: Labeling Comments and Marked-up Package Insert

Dear Dr. Harvey:

Reference is made to NDA 21-849 for Zegerid® (omeprazole) Capsules 20 mg and 40 mg, originally submitted on April 26, 2005. Reference is also made to the facsimile transmission of January 27, 2006 from Ms. Mary Lewis, Regulatory Project Manager, Division of Gastroenterology Products to Mr. Charles H. Davis of Santarus in which labeling comments and a marked-up package insert were forwarded.

We have the following responses to the various comments on the proposed container labels and package insert for Zegerid Capsules. We essentially concur with all of the comments and requests made by the Division with only a few exceptions which are discussed below. We would like to discuss these few exceptions with the Division review team in a telephone conference as soon as convenient.

A. GENERAL COMMENTS

1. **Ensure the font size of the letters comprising the established name on all labels and labeling is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.**

We here confirm that the font size of the letters comprising the established name on all labels and labeling will be at least one-half as large as the proprietary name.

We refer to the definition of an established name in the Federal Food Drug & Cosmetic Act [Section 502(e)(3)] which states the following:

As used in subparagraph (1), the term "established name", with respect to a drug or ingredient thereof, means (A) the applicable official name designated pursuant to section 508, or (B) if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient, except that where clause (B) of this subparagraph applies to an article recognized in the United States Pharmacopeia and in the Homeopathic Pharmacopeia under different official titles, the official title used in the United States Pharmacopeia shall apply unless it is labeled and offered for sale as a homeopathic drug, in which case the official title used in the Homeopathic Pharmacopeia shall apply.

[redacted]

Please refer to the revised container labels and physician sample carton labels in Section 1.14.1.1.

2. **Revise the statement "Directions for use: See..." to read** [redacted]

The reference to "Directions for use" is in compliance with 21 CFR 201.5. The regulation requires more information than [redacted] .. Therefore, we believe the labeling should still state, "Directions for use: See package insert for full prescribing information."

3. **The white font on the orange background may be difficult to read. Please utilize a darker background and/or revise the color combination to improve contrast and readability.**

We have increased the contrast and readability on the orange labels by utilizing black shadows on letters printed in white and increasing the font size. Please refer to Section 1.14.1.1 where revised container labels and physician sample carton labels are submitted.

4. **DMETS does not recommend use of the same color scheme (i.e., blue and orange) for both strengths. Despite the reversal of the colors, the similarities may increase the potential for selection errors.**

We agree to revise the colors for the Zegerid Capsule container labels so that the 20 mg container label is solid blue and the 40 mg container label is solid orange. Please refer to Section 1.14.1.1 where revised container labels and physician sample carton labels are submitted.

B. CONTAINER LABELS

1. **See General Comments A.1.a. through A.1.d.**

   Please refer to our responses to each of the items above.

2. **Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength. Thus, we request relocation of the product strength to appear immediately after or adjacent to the proprietary and established names, and away from the net quantity statement (see figure 1).**

   We agree to relocate the product strength so that it will appear immediately after or adjacent to the proprietary and established names. Please refer to Section 1.14.1.1 where revised container labels and physician sample carton labels are submitted.

3. **Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 capsules) to be in accordance with the Poison Prevention Act.**

   We here confirm that the closures are child resistant.

4. **Statement of Storage Conditions on Container Labels**

   As discussed in the e-mail message from Mr. Charles H. Davis to Ms. Mary Lewis on January 23, 2006 we are also revising the statement of storage conditions on the container labels to read as follows:

   "Store at 25°C (77°F) (see insert)."

   Similarly, the statement of storage conditions appearing on the physician sample carton label will be revised to read as follows:

   Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
   [see USP Controlled Room Temperature]

   In the original NDA the proposed container labels incorrectly stated, "[redacted]. The statement of storage conditions appearing in the proposed package insert is correct as originally submitted.

C. CARTON LABELING

See General Comments A.1.a. through A.1.d.

Please refer to our responses to each of the items above.

D. PACKAGE INSERT LABELING

1. PRECAUTIONS Section

In accordance with 21 CFR 201.57(f)(2), reprint the Information for Patients subsection at the end of the labeling.

The package insert will be revised to include the Information for Patients subsection at the end of the labeling as requested. Please refer to Section 1.14.1.3 for a copy of the revised package insert.

2. DOSAGE AND ADMINISTRATION Section

Include the established name of this drug product in the Dosage and Administration Section.

The package insert will be revised to include the established name in the Dosage and Administration section. However, could you please clarify the basis for this request?

3. NDA 21-849, Division edits 1/26/06.

The sponsor hereby agrees to incorporate all of the Division Edits transmitted in the January 27, 2006 facsimile with one exception discussed below.

4. PRECAUTIONS Section, Drug Interactions Subsection

Santarus is also revising the Drug Interactions subsection of the PRECAUTIONS section to include new information regarding concomitant administration of omeprazole and atazanavir and omeprazole and tacrolimus. This revision is being made so that the labeling for Zegerid will match revisions made in the labeling for Prilosec® (omeprazole) approved on January 26, 2006 (NDA 19-810/S-083). The following two sentences are included:

> Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir.
>
> Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

5. General Edits

The package insert is also revised to include the most recent editorial changes that were submitted in Amendment 0009 on January 4, 2006. Please refer to Section 1.14.1.5 Labeling History for a list of changes made.

Revised container labels, physician sample carton labels and the package insert are provided as follows:

Container Labels for Zegerid Capsules 20 mg, Bottles of 30
Container Labels for Zegerid Capsules 40 mg, Bottles of 30
Container Labels for Zegerid Capsules 20 mg, Physician Sample Bottles of 5
Container Labels for Zegerid Capsules 40 mg, Physician Sample Bottles of 5

Carton Labels for Zegerid Capsules 20 mg, Physician Samples Bottles of 5
(Cartons Contain 12 Bottles of 5 Capsules)
Carton Labels for Zegerid Capsules 40 mg, Physician Samples Bottles of 5
(Cartons Contain 12 Bottles of 5 Capsules)

Package Insert

Labeling History

If the Division agrees with all of the responses submitted here by the Sponsor, it may be possible to have the telecon previously scheduled for February 7, 2006 at 11:00 am EST (8:00 am PST) at an earlier time or, alternatively, to cancel it completely. If this is the case, we request that you notify us as soon as possible.

If you should have any questions regarding the information submitted, please contact Mr. Charles Davis, Senior Director, Regulatory Affairs for Santarus at telephone number: 858-314-5753, facsimile number: 858-314-5788 or e-mail: cdavis@santarus.com.

Sincerely,

Charles H. Davis, RAC
Senior Director, Regulatory Affairs

Virus-free Statement: This submission is virus free. The CD-ROM was scanned using Trend Micro OfficeScan Client for Windows XP/2000/NT, Program Version 6.0, VSApiNT Version 8.000.1001, TmFilter Version 8.000.0.1001, Virus Pattern File Number 3.183.00 (Trend Micro Inc). Additionally, our system is automatically updated with the latest virus definition patterns in order to ensure the best protection against viruses.

Lewis, Mary

From: Amanda Omlor [AOmlor@santarus.com]
Sent: Monday, January 30, 2006 9:05 PM
To: Lewis, Mary
Cc: Charley Davis
Subject: Response to fax dated Jan 27, 2006 (NDA 21-849)
Importance: High
Sensitivity: Confidential
Follow Up Flag: Follow up
Flag Status: Flagged

Hello Mary,

I am sending this on behalf of Charley Davis. In response to your facsimile of Friday, January 27, 2006, please see the enclosed files, consisting of the cover letter and the revised proposed labeling, including the package insert (in Word) and carton and container labels. The carton and container labels will follow in a second email due to restrictions on file size. The electronic submission will be sent via FedEx tomorrow (Amendment 0010).

Thank you,

Amanda M. Omlor, RAC
RA/QA Associate
Santarus, Inc.
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

858-314-5761 (direct)
aomlor@santarus.com

23 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

1.14.1.1 DRAFT CARTON AND CONTAINER LABELS

Zegerid® Capsules 20 mg/1100 mg and 40 mg/1100 mg will be made available in bottles containing 30 capsules and physician samples containing 5 capsules per bottle. Commercial product packaging will not include an outer carton. The physician samples will be made available in display cartons of 12 bottles per carton. The following draft display carton and container (bottle) labels are attached:

Display Carton Labeling

Zegerid® Capsules 20 mg/1100 mg – Physician Sample

Zegerid® Capsules 40 mg/1100 mg – Physician Sample

Container Labels

Zegerid® Capsules 20 mg/1100 mg – Physician Sample

Zegerid® Capsules 40 mg/1100 mg – Physician Sample

Zegerid® Capsules 20 mg/1100 mg – Commercial

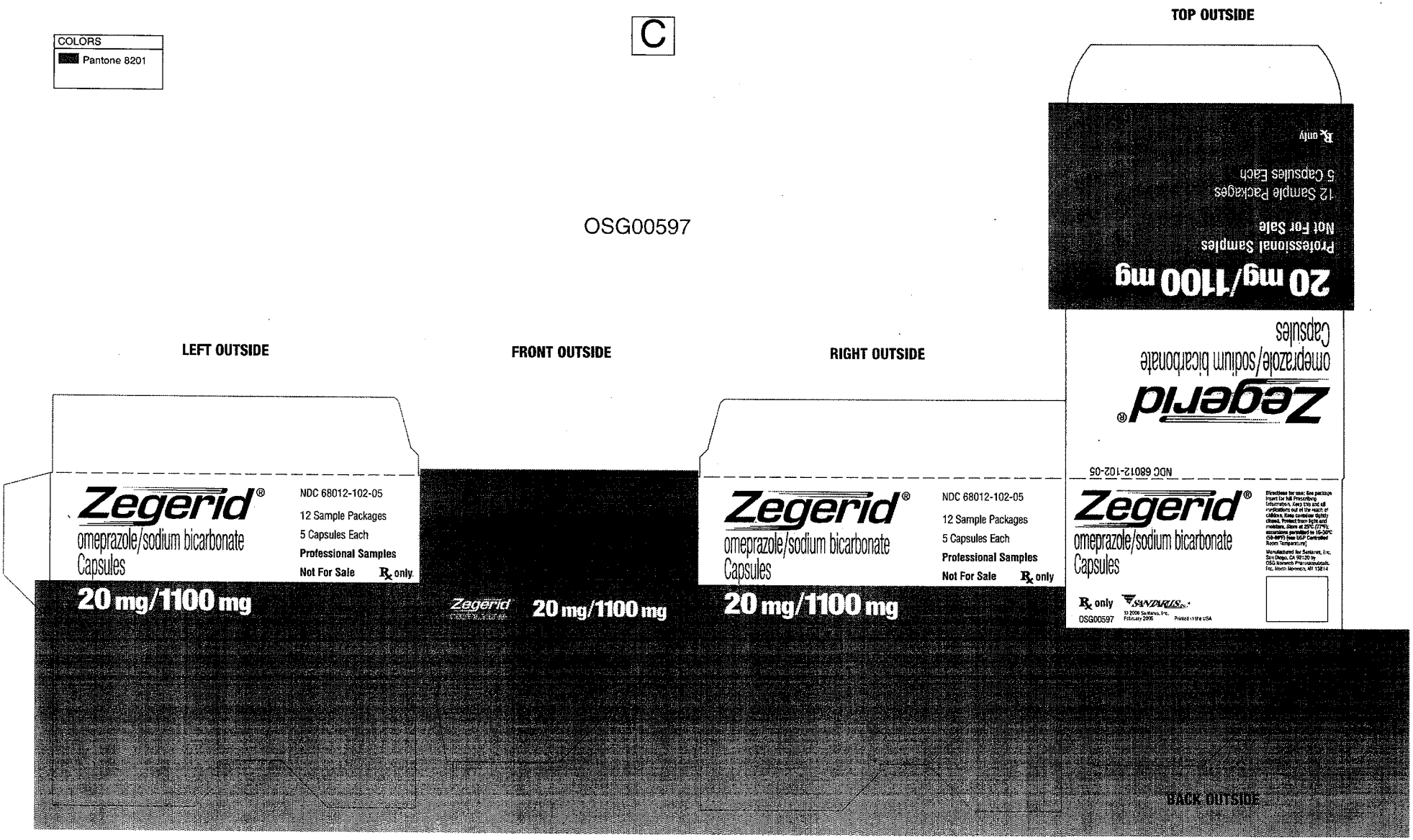
Zegerid® Capsules 40 mg/1100 mg – Commercial

COLORS

Pantone 8201

C

OSG00597



COLORS

Pantone 144C

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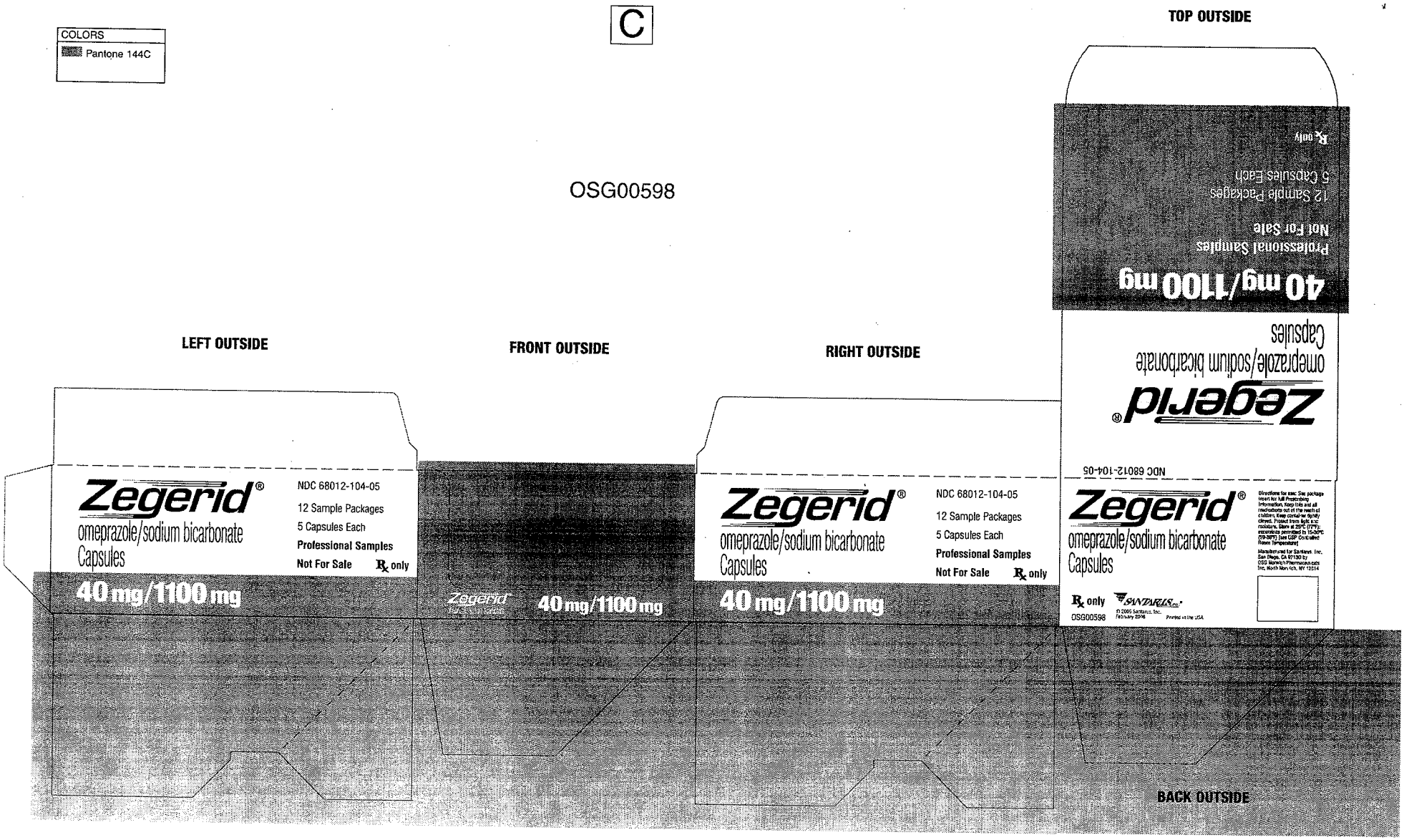
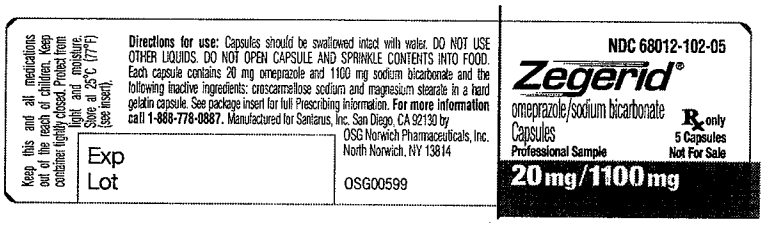
OSG00598

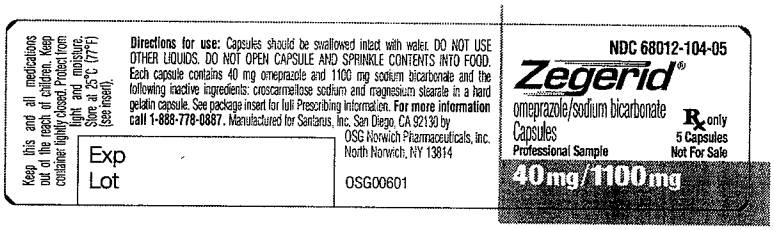


ZEG 20 & 40mg Labels 02/10/06

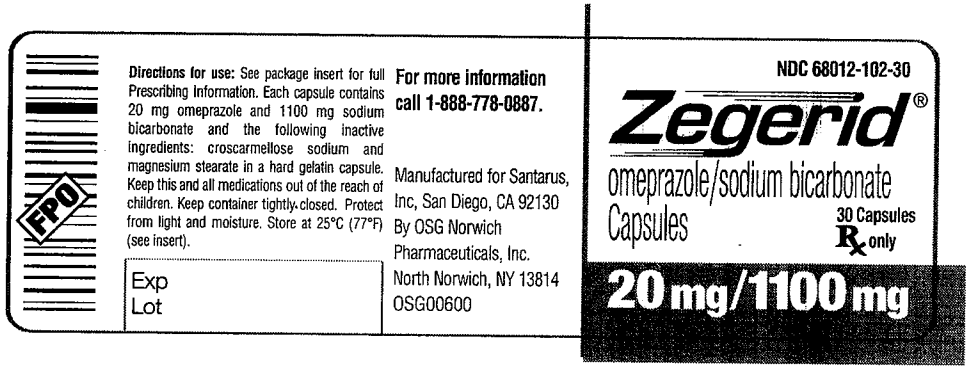
20 mg Sample Label



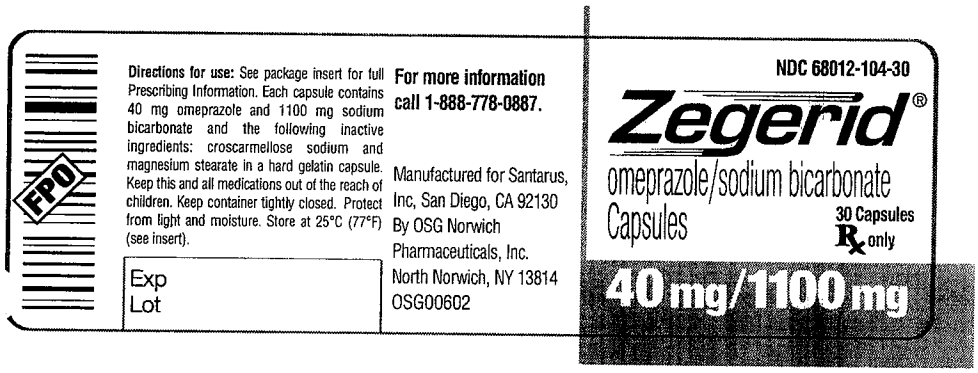
40 mg Sample Label



20 mg Commercial Label



40 mg Commercial Label



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 27, 2006

To: Charles Davis, RAC Senior Director, Regulatory Affairs	**From:** Mary M. Lewis, Regulatory Project Manager
Company: Santarus, Inc.	Division of Gastroenterology Products
Fax number: (858) 314-5788	**Fax number:** 301-796-9905
Phone number: (858) 314-5753	**Phone number:** 301-796-0941

Subject: NDA 21-849 Labeling Comments and Marked-up Pkg Insert

Total no. of pages including cover: 24

Comments:

Document to be mailed: ☐ YES ☑ NO

Attachment

The Agency has the following comments regarding your proposed label for NDA 21-849:

A. GENERAL COMMENTS

1. Ensure the font size of the letters comprising the established name on all labels and labeling is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

2. Revise the statement "Directions for use: See..." to read, "

3. The white font on the orange background may be difficult to read. Please utilize a darker background and/or revise the color combination to improve contrast and readability.

4. DMETS does not recommend use of the same color scheme (i.e. blue and orange) for both strengths. Despite the reversal of the colors, the similarities may increase the potential for selection errors.

B. CONTAINER LABELS

1. See General Comments A.1.a. through A.1.d.

2. Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength. Thus, we request relocation of the product strength to appear immediately after or adjacent to the proprietary and established name, and away from the net quantity statement (see figure 1).

3. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 capsules) to be in accordance with the Poison Prevention Act.

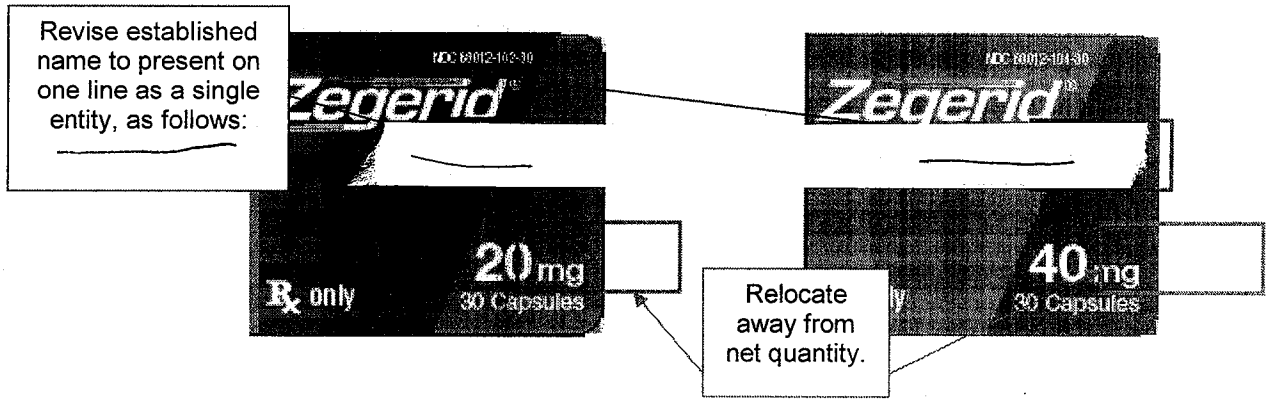


Figure 1

C. CARTON LABELING

See General Comments A.1.a. through A.1.d.

D. PACKAGE INSERT LABELING

1. PRECAUTIONS Section

In accordance with 21 CFR 201.57(f)(2), reprint the Information for Patients subsection at the end of the labeling.

2. DOSAGE AND ADMINISTRATION Section

Include the established name of this drug product in the Dosage and

Administration Section.

27 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

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

/s/

Mary Lewis
1/27/2006 11:48:13 AM
CSO

Mary Lewis
1/27/2006 11:52:24 AM
CSO

Lewis, Mary

From: Lewis, Mary
Sent: Friday, January 27, 2006 2:19 PM
To: Charles Davis (cdavis@santarus.com)
Cc:
Subject: Emailing: NDA 21-849 Proposed Label Track Changes 012506.doc

NDA 21-849
roposed Label Trac.

Hi:

Here is the proposed label with our track changes.

Mary

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____ Deliberative Process

21 Page(s) Withheld

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_X_ Draft Labeling

_____ Deliberative Process

1/25/06

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; WO22, M/S 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:**
December 7, 2005	January 31, 2006	05-0127-1 (NDA 21-849)
DOCUMENT DATE:	**PDUFA DATE:**	05-0135-1 (NDA 21-850)
April 26, 2005 (NDA21-849)	February 26, 2006 (NDA 21-849)	
May 25, 2005 (NDA 21-850)	March 26, 2006 (NDA 21-850)	

TO: Brian Harvey, MD
Director, Division of Gastroenterology Products, HFD-180

THROUGH: Alina R. Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Tina M. Tezky, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:	**NDA SPONSOR:** Santarus, Inc.
Zegerid® Omeprazole Capsules 20 mg and 40 mg **NDA#:** 21-849 **Zegerid®** Omeprazole Tablets (Chewable) 20 mg and 40 mg **NDA#:** 21-850	

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. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. 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 Diane Smith, project manager, at 301-827-3242.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; WO22, M/S 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 14, 2005

NDA#: 21-849 and 21-850

NAME OF DRUG: Zegerid® Omeprazole Capsules, 20 mg and 40 mg
Zegerid® Omeprazole Tablets (Chewable) 20 mg and 40 mg

NDA HOLDER: Santarus, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology Products (HFD-180) for a re-review of the proprietary name, Zegerid, regarding potential name confusion with other proprietary and/or established drug names. The proprietary name, Zegerid, was previously reviewed on June 30, 2005 (ODS consult #05-0127 and #05-0135). Zegerid Capsules and Zegerid Chewable Tablets are an extension of the Zegerid product line. Zegerid (Omeprazole Powder for Oral Suspension) 20 mg (NDA 21-636) was approved by the FDA on June 15, 2004 and Zegerid (Omeprazole Powder for Oral Suspension) 40 mg (NDA 21-706) was approved on December 21, 2004.

PRODUCT INFORMATION
Zegerid (omeprazole) is a proton-pump inhibitor indicated for short-term treatment of active duodenal ulcer, short-term treatment (4-8 weeks) of active benign gastric ulcer, treatment of heartburn and other symptoms associated with GERD, short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and to maintain healing of erosive esophagitis. The usual dose of Zegerid is 20 mg to 40 mg by mouth once daily. Zegerid Capsules and Zegerid Chewable Tablets are supplied in bottles of 30 capsules and 30 tablets, respectively.

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

Since the powder for oral suspension formulation is currently marketed, DMETS searched the FDA Adverse Event Reporting System for cases of medication errors associated with Zegerid using the preferred terms, "medication error, accidental exposure, accidental overdose, overdose, underdose, treatment noncompliance and pharmaceutical product complaint. One medication error report was discovered concerning name confusion between Zestril and Zegerid. This error was initiated by the handwritten misspelling of Zegerid as "Zegrid". Both Zestril and Zegerid are administered orally once daily and have overlapping dosage strengths (20 mg, 40 mg), increasing the potential for error. In this case, the wrong medication reached the patient, but was not administered. The error was discovered when the nurse called the

pharmacist with concerns about giving Zestril to an already hypotensive patient. The Institute of Safe Medication Practices (ISMP) also recently published an article citing this error[1]. DMETS will continue to monitor for complaints and errors between the proprietary names Zegerid and Zestril.

The newly proposed dosage forms (capsules and chewable tablets) are also available in 20 mg and 40 mg strengths. Thus, we anticipate similar types of confusion with the newly proposed dosage forms of Zegerid.

III. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[2,3] as well as several FDA databases[4] 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 conducted[5]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

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 were 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 did not have concerns with the name, Zegerid, in regard to promotional claims.

2. Since the initial review conducted on June 30, 2005, the Expert Panel did not identify any proprietary names that were thought to have the potential for confusion with Zegerid.

3. One name, Zestril, was identified through AERS reporting system and is listed in Table 1 (see page 4), along with the available dosage forms and usual dosage.

---

[1] Misspelling leads to mix-up. ISMP Safety Alert! December 15, 2005, 10(25).
[2] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.
[4] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.
[5] www location http://www.uspto.gov/tmdb/index.html.

Table 1: Potential Sound-Alike/Look-Alike Names Identified for Zegerid

Product Name	Dosage [illegible] name	[illegible]	Other**
Zegerid*	Omeprazole [illegible] 20 mg, 40 mg* Omeprazole Tablets [illegible] 20 mg, 40 mg	[illegible] daily	
Zestril Rx	Lisinopril Tablets 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg	5 mg – 40 mg once daily.	LA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

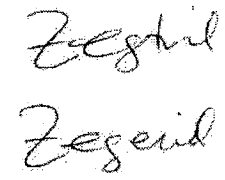
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine 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 by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

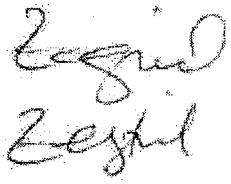
Zegerid Capsules and Chewable Tablets are a product line extention of Zegerid Powder for Oral Suspension. When reviewing the new dosage forms, the expert panel did not identify any names of potential concern. The introduction of these two dosage forms does not pose any new safety risks as the capsules and chewable tablets will be available in the same strengths as the powder for oral suspension. An AERS search was conducted to determine if there have been any reported cases of errors with the name or labeling/packaging of this product. AERS uncovered one name of concern, Zestril, which was not evaluated in our previous reviews of the proprietary name Zegerid and will be discussed below.

A search of AERS identified one case where Zestril was identified as having look-alike potential with Zegerid. Zestril (omeprazole) is a long-acting angiotensin converting enzyme inhibitor indicated for use in hypertension, heart failure, and hemodynamically stable patients within 24 hours of acute myocardial infarction. Zestril is currently available as 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg tablets. The usual dose of Zestril is 5 mg – 40 mg once daily. Zestril and Zegerid contain the same number of letters (seven) and have four overlapping letters (ZESTRIL vs. ZEGERID), which contribute to their look-alike similarities. The letters ("S" vs. "G") can look similar when scripted in the middle of a word (see writing sample, page 5). However, the second "E" in Zegerid gives the name a longer appearance and provides a visual distinction from Zestril. To compound the potential for confusion between the two drug names, they share the same dosage form (oral: capsules, chewable tablets vs. tablets), route of administration (oral), dosage frequencies (once daily), and have overlapping product strengths (20 mg, 40 mg). However, the reported error was initiated by the misspelling of Zegerid as "Zegrid". The omission of the second "E" in Zegerid, gives the name a shorter appearance and a greater visual similarity to Zestril (see sample, page 5). Therefore, at this time, DMETS has no objections to the use of the name Zegerid for the

capsules and chewable tablets. DMETS will continue to monitor for further confusion between the names Zestril and Zegerid.



Zestril vs. Zegerid



"Zegrid" vs. Zestril

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels as well as the carton and insert labeling proposed for Zegerid Capsules and Chewable Tablets, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. ZEGERID CAPSULES

1. GENERAL COMMENTS

a. Ensure the font size of the letters comprising the established name on all labels and labeling is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

b. Revise the statement

c. The white font on the orange background may be difficult to read. Please utilize a darker background and/or revise the color combination to improve contrast and readability.

d. DMETS does not recommend use of the same color scheme (i.e. blue and orange) for both strengths. Despite the reversal of the colors, the similarities may increase the potential for selection errors.

2. CONTAINER LABELS

a. See General Comments A.1.a. through A.1.d.

b. Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength. Thus, we request relocation of the product strength to appear immediately after or adjacent to the proprietary and established name, and away from the net quantity statement (see figure 1).

c. Ensure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 capsules) to be in accordance with the Poison Prevention Act.

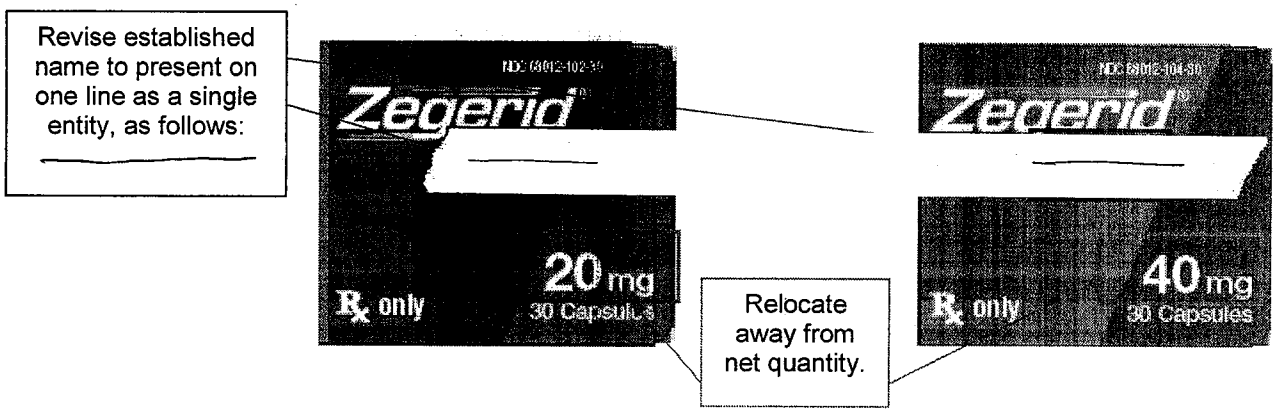


Figure 1

3. CARTON LABELING

See General Comments A.1.a. through A.1.d.

4. PACKAGE INSERT LABELING

a. PRECAUTIONS Section

In accordance with 21 CFR 201.57(f)(2), reprint the Information for Patients subsection at the end of the labeling.

b. DOSAGE AND ADMINISTRATION Section

Include the established name of this drug product in the Dosage and Administration Section.

B. ZEGERID CHEWABLE TABLETS

1. GENERAL COMMENTS

a. See Zegerid Capsules General Comments A.1.c, and A.1.d.

b. Ensure the font size of the letters comprising the established name on all labels and labeling is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance. Additionally, revise and center the established name to appear on one line as a single entity below the proprietary name (see figure 2) on all labels and labeling as follows:

omeprazole tablets (chewable)

1 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

3. CARTON LABELING

See Zegerid Chewable Tablets General Comments B.1.a and B.1.b.

4. PACKAGE INSERT LABELING

See Zegerid Capsules Package Insert Labeling Comments A.4.a. and A.4.b.

2. CONTAINER LABELS

a. See Zegerid Chewable Tablets General Comments B.1.a and B.1.b.

b. See Zegerid Capsules Container Label Comments A.2.b. and A.2.c.

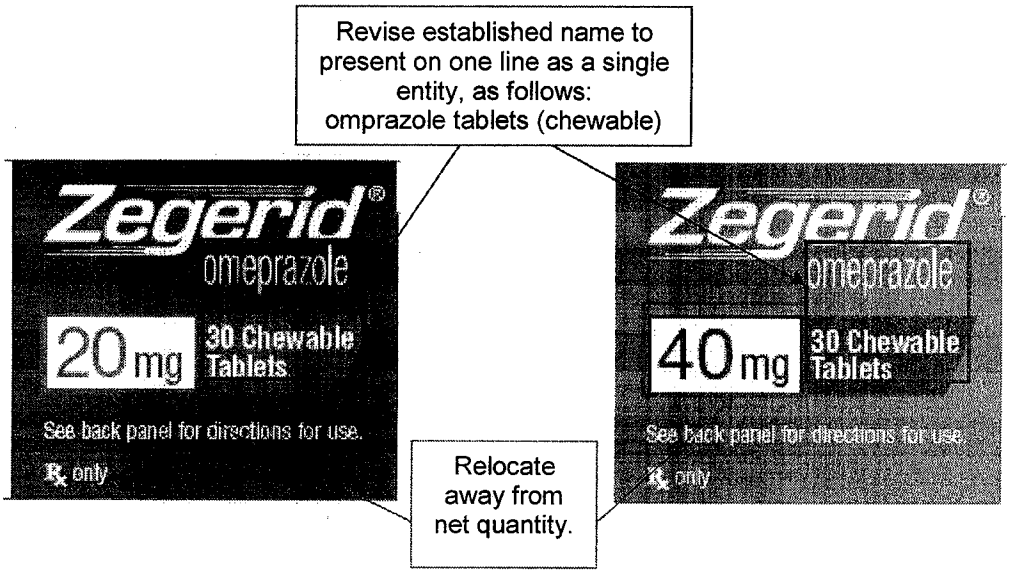


Figure 2

c. Ensure the proposed quantity of chewable tablets to be included in the Professional Sample is not too large. The current presentation does not indicate a net quantity; the sponsor just put an "X" immediately before "Chewable Tablets" on the principle display panel of the Professional Sample labeling. Remove the "X" and ensure the net quantity is away from the product strength and the established name is revised as recommended in comment B.1.b. (see figure 3).

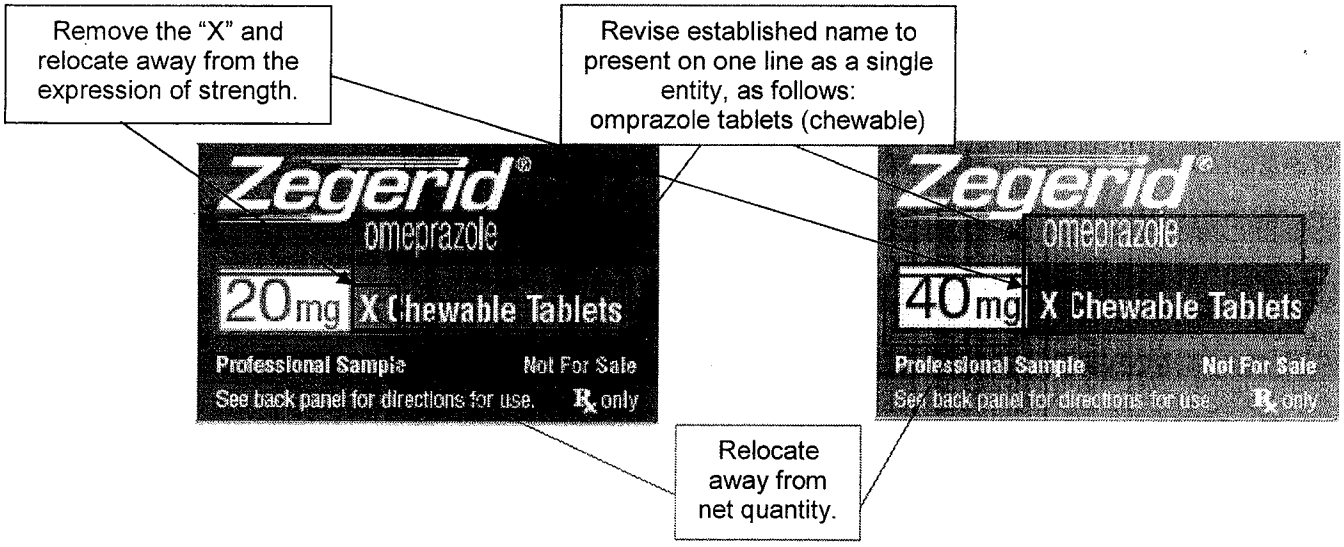


Figure 3

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/s/

Tina Tezky
1/24/2006 04:14:14 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/24/2006 04:24:24 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/25/2006 10:25:16 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/25/2006 11:30:36 AM
DRUG SAFETY OFFICE REVIEWER

Internal Consult

*** Pre-decisional Agency Information ***

To: Mary Lewis, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Debi Tran, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: January 17, 2006

Re: Consult request for product labeling

Zegerid® (omeprazole) Capsules and Powder for Oral Suspension

NDA 21-849

Thank you for consulting DDMAC on the proposed package insert and container labeling. The following comments are based on the version dated April 26, 2005, found in the electronic document room. If you have any questions, please contact me at 301-796-0633.

PACKAGE INSERT

CLINICAL STUDIES

Duodenal Ulcer Disease (page 5):

> "*Complete* daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had *complete* relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$)." (emphasis added)

Erosive Esophagitis (page 8):

> "*Complete* daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with omeprazole than in those taking placebo or histamine H2-receptor antagonists." (emphasis added)

> "*Complete* daytime and nighttime heartburn relief occurred significantly faster ($p < 0.01$) in patients treated with omeprazole than in those taking placebo or histamine H2-receptor antagonists." (emphasis added)

We recommend [redacted] because it [redacted]

Gastroesophageal Reflux Disease (page 7):

The title of Table 7 is "Successful Symptomatic Outcome." We recommend [redacted] in prescription drug advertising, especially when targeting the consumer audience.

PRECAUTIONS

General (page 10):

> "Zegerid contains 1680 mg (20 mEq) of sodium bicarbonate. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia."

Should a similar statement also appear in the Contraindications section of the proposed package insert? For example, "Zegerid is contraindicated in patients with metabolic alkalosis and hypocalcemia."

In addition, we note that the precautionary statement "This [i.e., Zegerid contains 460 mg sodium] should be taken into consideration for patients on a sodium-restricted diet" is included in the approved Zegerid package insert (NDA 21-636), but was omitted from this draft label.

Carcinogenesis, Mutagenesis, Impairment of Fertility (page 11):

[redacted]

Pregnancy (page 12):

[redacted]

Is it necessary to present the above statements in capital letters? We note no techniques were implemented to draw attention to identical statements in the approved Zegerid package insert (NDA 21-636).

Nursing Mothers (page 13):

We note the following statement, present in the approved Zegerid package insert (NDA 21-636), was omitted from this draft label:

[redacted]

Pediatric Use (page 13):

> "*Clinical studies have been conducted evaluating omeprazole in pediatric patients.* There are no adequate and well-controlled studies in pediatric patients with ZEGERID." (emphasis added)

[redacted] We also note that the first sentence is not present in the approved Zegerid package insert (NDA 21-636).

[redacted]

ADVERSE REACTIONS

On page 13:

> "Omeprazole was *generally well tolerated* during domestic and international clinical trials in 3096 patients." (emphasis added)

The term "generally well tolerated" can be used in promotion to minimize the overall risks associated with the drug. We recommend

On page 14:

> "A controlled clinical trial conducted in 359 critically ill patients, comparing ZEGERID 40 mg once daily to IV cimetidine 1200 mg/day for up to 14 days,

We note that certain adverse events were greater in the Zegerid treatment group versus the cimetidine treatment group e.g., thrombocytopenia (10.1% vs. 6.1%), atrial fibrillation (6.2% vs. 3.9%), pyrexia (20.2% vs. 16%), hypertension NOS (7.9% vs. 3.3%), hypotension NOS (9.6% vs. 6.6%), etc. . . .

On page 16:

> "Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole."

Although the above statement refers to adverse events in trials conducted with omeprazole or since the drug was marketed, the statement also promotes an off-label use because the proposed indications for Zegerid do not include Zollinger-Ellison syndrome. We recommend

On page 18:

According to Table 14, the recommended dose for benign gastric ulcer is 40 mg once daily for 4-8 weeks regardless of the ulcer size. However, on page 6, the Clinical Studies, Gastric Ulcer section states "For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was

significantly more effective than 20 mg at 8 weeks."

The Indications and Usage section, on page 9, communicates "Controlled studies do not extend beyond 12 months" for maintenance of healing of erosive esophagitis.

CONTAINER LABELING

We have reviewed the draft container labeling for Zegerid and have no comments at this time.

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/s/

Debi Tran
1/17/2006 06:22:19 PM
DDMAC REVIEWER

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MEMORANDUM

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

DATE: January 4, 2006

TO: Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products, DGP

FROM: Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-849 (Zegerid® Omeprazole Capsules, and NDA 21-850 (Zegerid® Omeprazole Chewable Tablets, Sponsored by Santarus Inc.

At the request of DGP, the Division of Scientific Investigations audited the analytical portions of the following bioequivalence studies, performed at [redacted]. DSI plans to inspect the clinical portions of the studies at [redacted]. This review covers only the analytical portions of the studies

Protocol OME-IR(CAP)-C02, Analytical #AA20649: "A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Capsules 40 mg with Prilosec® Delayed Release Capsules 40 mg in Healthy Subjects"

Protocol OME-IR(TAB)-C02, Analytical AA20651-01: "A Comparison of the Pharmacokinetics and Pharmacodynamics of Zegerid® Immediate-Release Chewable Tablets 40 mg with Prilosec® Delayed Release Capsules 40 mg in Healthy Subjects"

Following the inspection at [redacted], Form 483 was issued. The objectionable observation and our evaluation are as follows:

[redacted]:

1. **With respect to studies AA20649 and AA20651: The pre-study method validation of accuracy and stability during freeze-thaw cycles and long-term frozen storage failed to use freshly-prepared calibrators or references. The freeze/thaw stability evaluation used month-old calibrators, and the long-term stability evaluation used year-old calibrators.**

A new external validation of stability during handling and storage was necessary for evaluation of both studies, because both calibrators and quality control (QC) samples in plasma matrix were prepared in bulk, and stored frozen with the study samples for up to four months. Any chemical instability or changes in extraction efficiency would not be detectable by comparing QCs to calibrators stored with them. However, [redacted] completed a satisfactory validation of freeze-thaw and long-term stability during the inspection.

Conclusions:

DSI recommends that the analytical data from studies OME-IR(CAP)C02 and OME-IR(TAB)C02 are acceptable for review. The results of the clinical site inspection will be provided as soon as possible.

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

Michael F. Skelly, Ph.D.
Pharmacologist

Final Classification:
VAI - [redacted]

Recommendation: Pharmacokinetic data from studies OME-IR(CAP)C02 and OME-IR(TAB)C02 are acceptable for review.

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya
HFD-48/CF
DGP (formerly HFD-510)/NDAs 21-849 and 21-850/Lewis
HFR-SW3515/Mueller
Drafted: MFS 11/23/05
Edits: MFS 12/19/05 and 1/4/06 (Re: Mont)
DSI: 5626, 5636; O:\BE\EIRCover\21849SANx.ome.doc
FACTS: 662260

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/s/

Michael Skelly
1/6/2006 03:47:15 PM
PHARMACOLOGIST
Paper original signed by Skelly 1/4/06 and by Viswanathan 1/6/06

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Lewis, Mary

From: Viswanathan, CT
Sent: Friday, January 06, 2006 3:03 PM
To: Lewis, Mary
Subject: RE: NDA 21-849, DSI Consult, Zegerid Capsules (omeprazole) 40 mg; also NDA 21-850

Analytical reports for both NDAs are completed and will be forwarded to you at the end of next week. As I said the clinical portions for both applications can only be scheduled for ——— We will keep you posted.
Thanks..

-----Original Message-----
From: Lewis, Mary
Sent: Friday, January 06, 2006 2:56 PM
To: Viswanathan, CT
Cc: Lewis, Mary
Subject: RE: NDA 21-849, DSI Consult, Zegerid Capsules (omeprazole) 40 mg; also NDA 21-850

+ then NFO-180 was notified the inspection wouldn't happen until ———
MML

Hi:

Thank you for the voice message.

My biopharm person needs both reviews as soon as they are available. Please "cc" me or send me the analytical review as soon as possible.

I understand from your voice message the clinical portion is not done yet, that it will take place in ——— ———. Please send me that report as soon as it is completed.

The other omeprazole DSI consult that we sent is for NDA 21-850, and that PDUFA date is 3/26/06. I believe that inspection is also ———

Thank you.

Mary

-----Original Message-----
From: Viswanathan, CT
Sent: Friday, January 06, 2006 2:08 PM
To: Lewis, Mary
Subject: RE: NDA 21-849, DSI Consult, Zegerid Capsules (omeprazole) 40 mg

Left a voice mail today..
Thanks..

-----Original Message-----
From: Lewis, Mary
Sent: Tuesday, January 03, 2006 5:26 PM
To: Viswanathan, CT
Cc: Lewis, Mary
Subject: NDA 21-849, DSI Consult, Zegerid Capsules (omeprazole) 40 mg

Hi:

I need to ask for your assistance. The Gastroenterology Division sent you a DSI Consult on 6/13/05. My biopharm reviewer understands that the site has been inspected, and I wanted to know if you could tell me who the DSI reivewier is that this was assigned to. I would like to call him/her and see when we can expect the report to be completed.

The PDUFA is 2/26/06.

Thank you for your assistance.

Mary

Mary M. Lewis, RN, BSN
Regulatory Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9905
email: lewisma@cder.fda.gov

Lewis, Mary

From: Charley Davis [CDavis@santarus.com]
Sent: Monday, January 23, 2006 5:03 PM
To: Lewis, Mary
Subject: Container Labels for NDA 21-849, Zegerid Capsules 20 mg and 40 mg
Follow Up Flag: Follow up
Flag Status: Flagged

Hi Mary,

As I mentioned earlier today the draft container labels submitted in NDA 21-849 for Zegerid Capsules 20 mg and 40 mg (trade containers of 30 and physician sample containers of 5) contain an incorrect statement on the storage conditions. The draft labels incorrectly state, "Store between [redacted]." The correct statement, in accordance with the Agency's Guidance document on stability testing and with Module 3 of the NDA , should be "Store at 25°C (77°F) (see insert)." The conclusions stated in the stability section of the NDA in Module 3 regarding drug product storage conditions and the storage statement in the draft package insert are correct as submitted - it is only the trade container labels, physician sample container labels, and physician sample display cartons that are affected.

We will submit appropriate revised draft containers labels as soon as they are available. The purpose of our telephone calls on Friday (1/20/06) and earlier today (1/23/06) was to determine the status of the review on the container labels. Are there any comments or questions from any members of the review team regarding the draft container labels for the Zegerid Capsules? We are hoping to finalize the text of the container labels soon. If there are any questions or comments from the review team we could incorporate any such changes at the same time.

Please let us know as soon as possible if there are any questions, comments or requests regarding the draft container labels.

Thanks very much,

Charley Davis

Charles H. Davis
Senior Director, Regulatory Affairs
Santarus, Inc.
10590 West Ocean Air Dr., Suite 200
San Diego, CA 92130
Office: 858-314-5753
Mobile: 949-683-0805
cdavis@santarus.com

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2005

To: Charles Davis	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Santarus	Division of Gastroenterology Products
Fax number: (858) 314-5788	**Fax number:** (301) 443-9285
Phone number: (858) 314-5733	**Phone number:** (301) 796-1008

Subject: Information Request for NDA 21-849, Zegerid Capsules 20mg and 40mg

Total no. of pages including cover: 2

Comments:

Please provide an annotated package insert in Word format highlighting the proposed changes from the currently approved Zegerid 20 and 40 mg powder for oral suspension to the combined package insert for Zegerid 20 and 40 mg powder for oral suspension and capsules. Thanks

Document to be mailed: ☐ YES ☑ NO

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/s/

Brian Strongin
12/23/2005 01:26:34 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Diane Smith
Division of Medication Errors and Technical Support
White Oak, Building 22, Room 4421
Silver Spring, MD

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Gastroenterology Products
W.O., Bldg. 22, Room 5102
Mary M. Lewis, Regulatory Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/6/05		21-849	Re-review of NDA tradename	4/26/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zegerid (omeprazole) Capsules, 20 & 40 mg	Standard	Proton Pump Inhibitor	January 31,2006

NAME OF FIRM: Santarus, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 21-849 Zegerid (omeprazole) Capsules, 20 and 40 mg was submitted electronically and may be found in the EDR (pathway - N21849, document date: 26 APR 2005 in the Labeling folder.) The PDUFA goal date is 2/26/06 and we anticipate approving this application. In your review of June 30, 2005, regarding this same application, you requested a re-review of the name prior to the NDA approval.

SIGNATURE OF REQUESTOR
Mary M. Lewis, RPM
301-796-0941

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Mary Lewis
12/6/2005 03:28:21 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849

INFORMATION REQUEST LETTER

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 April 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Capsules 20 mg and 40 mg.

We are reviewing the Biophamaceutical 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.

For study OME-IR (CAP) -C02, the reported bioequivalence (BE) assessment with 90% confidence intervals (CIs) using 2-1-sided tests for comparing postmeal (Day 8) vs. premeal (Day 7) of Zegerid 40 mg capsules in 18 subjects could not be verified/reproduced, i.e., 43.07 - 71.45 for C_{max}, 70.21 – 85.70 for AUC_{0-t}, and 70.67 – 85.93 for $AUC_{0-\infty}$ (Post-Text Table 15.4-14, p.79).

For data analysis confirmation, please provide:

1) The analysis procedure if WinNonln was used, or
2) Control file if SAS was used for model, design (parallel ?), random factors, etc.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at 301-796-0941.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
12/6/2005 01:07:28 PM

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CONSULTATION RESPONSE

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

DATE RECEIVED:	DESIRED COMPLETION DATE:	ODS CONSULT #:
May 23, 2005 (NDA 21-849)	January 15, 2006	Zegerid: 05-0127
June 9, 2005 (NDA 21-850)		Zegerid Chewable Tablets: 05-0135
DATE OF DOCUMENT:	**PDUFA DATE:**	
April 26, 2005 (NDA 21-849)	February 26, 2006 (NDA 21-849)	
May 25, 2005 (NDA 21-850)	March 26, 2006 (NDA 21-850)	

TO: Brian Harvey, MD
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Mary Lewis
Project Manager, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME:	NDA SPONSOR: Santarus, Inc.
Zegerid (Omeprazole Capsules) 20 mg and 40 mg **NDA#:** 21-849 **Zegerid** (Omeprazole Chewable Tablets) 20 mg and 40 mg **NDA#:** 21-850	

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Zegerid. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA or ANDA. A re-review of the name prior to NDA or ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

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

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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 30, 2005

NDA#: Zegerid Capsules (NDA 21-849) and Zegerid Chewable Tablet (NDA 21-850)

NAME OF DRUG: Zegerid (Omeprazole Capsules) 20 mg and 40 mg
Zegerid (Omeprazole Chewable Tablets) 20 mg and 40 mg

NDA HOLDER: Santarus, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for assessment of the proprietary name, Zegerid, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

Zegerid Capsules and Zegerid Chewable Tablets are extensions of the Zegerid product line. Zegerid (Omeprazole Powder for Oral Suspension) 20 mg (NDA 21-636) was approved June 15, 2004 and the Zegerid (Omeprazole Powder for Oral Suspension) 40 mg (NDA 21-706) was approved December 21, 2004.

PRODUCT INFORMATION

Zegerid is a proton-pump inhibitor indicated for short-term treatment of active duodenal ulcer, short-term treatment (4-8 weeks) of active benign gastric ulcer, treatment of heartburn and other symptoms associated with GERD, short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, maintain healing of erosive esophagitis. The usual dose of Zegerid is 20 mg to 40 mg by mouth once daily. Zegerid Capsules and Zegerid Chewable Tablets are supplied in bottles of 30 capsules and 30 tablets respectively.

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 databases[3] for existing drug names which sound-alike or

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[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, and the electronic online version of the FDA Orange Book.

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 conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. 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 (EPD)

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(s) were 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 proprietary name, Zegerid, acceptable from a promotional perspective.

2. The Expert Panel did not identify any proprietary names that were thought to have the potential for confusion with Zegerid.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name 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 by the Expert Panel (EPD).

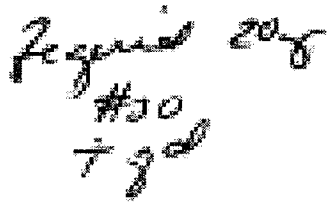
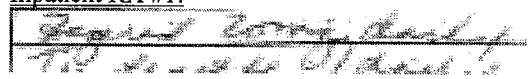
C. PRESCRIPTION ANALYSIS STUDIES

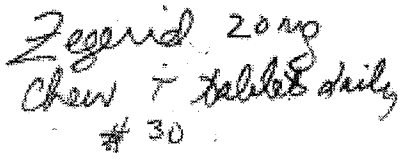
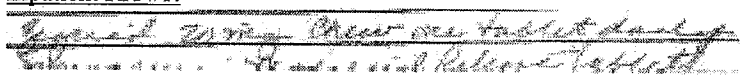
1. Methodology:

Two sets of three (inpatient written, outpatient written, and verbal) studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Zegerid Capsules and Chewable Tablets with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study set employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders and two outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zegerid Capsules and Chewable Tablets (see below). These prescriptions were optically scanned and one prescription was delivered to a

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

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
Outpatient RX #1: 	"The first one is Zegerid 20 mg. She is take that daily. Give her 30."
Inpatient RX #1: 	

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX #2: 	"First prescription is Zegerid 20 mg. Chew one tablet daily. Dispense 30."
Inpatient RX #1: 	

2. Results:

One respondent from inpatient study #1 misinterpreted the proposed name as Zagam. One respondent from verbal study #1 misinterpreted the proposed name as Zomig. One respondent from inpatient study #2 misinterpreted the proposed name as Zestril. Zagam, Zomig, and Zestril are all currently marketed U.S. products. One respondent from outpatient study #1 misinterpreted the proposed name as Tequid. Tequid could sound and look similar to the currently marketed product Tequin. See attachments A and B for the complete listing of interpretations from the verbal and written studies

D. ADVERSE EVENT REPORTING SYSTEM (AERS)

DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) for medication errors associated with Zegerid. The preferred terms "Medication Error," "Accidental Overdose," "Overdose NOS," and "Pharmaceutical Product Complaint," were used. DMETS did not identify any cases of medication errors associated with Zegerid or name confusion with the names identified from the prescription analysis study (Zagam, Zestril, Zomig, and Tequin).

E. SAFETY EVALUATOR RISK ASSESSMENT

Zegerid Capsules and Zegerid Chewable Tablets are a product line extension of Zegerid Powder for Oral Suspension. The introduction of these dosage forms do not pose any new safety risks as the capsule and tablets will be available in the same strengths as the powder for oral suspension. Additionally, an AERS search was conducted to determine if there have been any reported cases of name confusion since Zegerid's introduction into the marketplace. The search did not uncover any reported errors with the name or labeling/packaging of this product. When reviewing the new dosage forms, the expert panel did not identify any names of potential concern. However, the prescription studies uncovered three names of concern (Zagam, Zomig, and Zestril) that were not evaluated in our initial review of Zegerid with the powder for oral suspension.

In a review of the three names identified as potential look-alikes from the prescription studies it appears that none of them pose a risk as they lack substantial look-alike and/or sound-alike similarities and differ in indication and usual dose. Additionally, to date we have not received any postmarketing cases of confusion between Zegerid and the aforementioned names. Thus, the names appear to safely co-exist in the marketplace.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Zegerid Capsules and Chewable Tablets, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. ZEGERID CAPSULES

1. GENERAL COMMENTS

a. Relocate the net quantity so that it does not appear in close proximity to the product strength.

b. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name and center the established name below the proprietary name to increase the prominence of the established name.

c. Remove the statement, "See back panel for directions for use," from principal display panels. The back panel provides no instructions for use; it simply refers you to the package insert.

d. Revise the "Directions for use," statement to read, " ———— See package insert."

e. This packaging configuration (5 capsule bottles and 30 capsule bottles) appear to be unit-of-use. Please ensure these bottles utilize child-resistant closures in accordance with the PPA.

f. DMETS notes that the color scheme used for both the 20 mg and 40 mg capsules are the same. The color is primarily blue with orange accents for 20 mg and primarily orange with blue accents for 40 mg. The use of the same color scheme, but in an inverted fashion may increase the likelihood of a selection error between the two products. Revise accordingly.

g. Revise the established name to read " ———— " on all labels and labeling for Zegerid Capsules.

2. CONTAINER LABEL (20 mg and 40 mg Capsules, Trade and Sample)

   a. See General Comments A-1-a through A-1-g.

   b. Insert the statement, "Rx Only," on the principal display panel.

B. ZEGERID CHEWABLE TABLETS

1. GENERAL COMMENTS

   a. Relocate the net quantity so that it does not appear in close proximity to the product strength.

   b. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name and center the established name below the proprietary name to increase the prominence of the established name.

   c. Remove the statement, "See back panel for directions for use," from principal display panels. The back panel provides no instructions for use; it simply refers you to the package insert.

   d. Revise the "Directions for use," statement to read, "Usual dosage: See package insert."

   e. This packaging configuration (5 tablet bottle and 30 tablet bottle) appear to be unit-of-use. Please ensure these bottles utilize child-resistant closures in accordance with the Poison Prevention Act.

   f. DMETS notes that the color scheme used for both the 20 mg and 40 mg tablets are the same. The color is primarily blue with orange accents for 20 mg and primarily orange with blue accents for 40 mg. The use of the same color scheme, but in an inverted fashion may increase the likelihood of a selection error between the two products. Revise accordingly.

   g. Revise the established name to read "Omeprazole Tablets (Chewable)," on all labels and labeling for Zegerid Chewable Tablets.

2. CONTAINER LABEL (20 mg and 40 mg Chewable Tablets, Trade and Sample)

   The dosage form, "Tablets (Chewable)," should be presented juxtapose to the established name.

3. INSERT LABELING

   a. PRECAUTIONS Section, Information for Patients Section

      In accordance with 21 CFR 201.57(f)(2), reprint the Information for Patients subsection at the end of the labeling.

   b. DOSAGE AND ADMINISTRATION Section

      DMETS questions the need for the "For Additional Information" Column in Table 14. All information required for accurate dosing of Zegerid should be included in the Dosage and Administration section. Revise accordingly.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Zegerid. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA/ANDA. A re-review of the name prior to NDA/ANDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. 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 Diane Smith, project manager, at 301-827-1998.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Kim-Jung, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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Attachment A

Outpatient Written #1	Inpatient Written #1	Verbal #1
Fegerid	Agalert	Fegerid
Fegerid	Agera	Fegerid
Fegerid	Ageret	Fegired
Fegerid	Agura (or Agora) (or Accura)	Fegred
Fegerid	Anura	Fegrid
Fegerid	Cygoret	Fegrid
Fegerid	Fegerist	Tegirid
Fegeriel or Zegerial	Fiorid	Tegred
Fegeril	Iura	Tegred
Fegurid	Xygura	Tegrid
Figerid	Zagam	Tegrid
Figeride	zagaret	Tigrid
Figuid	Zagaret	Zegerid
Tegrerid	Zagaret	Zegerid
Tequid	Zagaret	Zegerid
Zegerid	Zagaret	Zegired
Zegerid	Zagered	Zegrid
Zegerid	Zangara	Zegrid
Zegerid	Zyar	Zeguid
Zegerid	Zygara	Zegurid
Zegerid	Zygara	Zequid
Zegeriel	zygaret	Zomig
Zequid	Zygora	
Zequid	Zygora	
Zergerid	Zygora	Appears This Way
	Zyurid	On Original

Attachment B

Verbal #2	Inpatient Written #2	Outpatient Written #2
Segeret	Zegerid	Zegerid
Xegerit	Zegerid	Zegerid
Zegared	Zegired	Zegerid
Zegaret	Zegreid	Zegerid
Zegarit	Zegreid	Zegerid
Zegarit	Zegreid	Zegerid
Zegarit	Zegrid	Zegerid
Zegarit	Zegrid	zegerid
Zegeret	Zegrid	Zegerid
zegerid	Zegried	Zegerid
Zegerid	Zegried	Zegerid
Zegerit	Zegried	Zegerid
Zegerit	Zegrud	Zegerid
Zegerit	Zegruid	Zegerid
Zegerit	Zeguid	Zegerid
Zegerit	Zeguid	Zegerid
Zegerit	Zeguid	Zegerid
Zegerit	Zequid	Zegerid
Zegorit	Zestril	Zegried
Zegurit	Zigeid	Zeregrid
	Zigriad	
	Zigried	
	Zigrud	
	Ziguid	
	Ziguid	
	Ziquid	

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/s/

Kristina Arnwine
8/24/2005 05:43:48 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/25/2005 08:31:31 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/25/2005 10:39:58 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/25/2005 10:59:29 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849

INFORMATION REQUEST LETTER

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 April 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Capsules, 20 mg and 40 mg.

We are reviewing the Biopharmaceutical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

- Submit dissolution data on the biobatches used in the OME-IR (CAP)-C01 and OME-IR (CAP) C02 studies.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
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
8/5/05 12:53:00 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-849

Santarus, Inc.
Attention: Christine Simmons, PharmD
Vice President, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, California 92130

Dear Dr. Simmons:

Please refer to your April 26, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Capsules, 20 mg and 40 mg.

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 June 26, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

We would like to request the following information:

- A summary of post-marketing safety information for Zegerid suspension.

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

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
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/

Brian Strongin
7/7/05 01:05:41 PM

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: June 13, 2005

TO: C.T. Viswanathan, Ph.D.
Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Suresh Doddapaneni, Ph.D.
Pharmacokinetic Team Leader
Office of Clinical Pharmacology and Biopharmaceutics, HFD-180

FROM: Mary Lewis, Regulatory Project Manager, HFD-180

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-849
Zegerid Capsules (omeprazole) 40 mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
OME-IR (CAP)-C02		

[ ]

[ ]

____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by November 26, 2005 in order for us to meet our regulatory deadlines.

Should you require any additional information, please contact Mary Lewis at 301-827-7475.

Concurrence: (Optional)
Ruyi He, Medical Team Leader
Tien Mien Chen, Biopharmaceutics Reviewer

Suresh Doddapaneni, Ph.D.
Pharmacokinetic Team Leader
Office of Clinical Pharmacology and
Biopharmaceutics, HFD-180

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/s/

Suresh Doddapaneni
6/16/05 06:25:40 PM

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Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-849

Name of Drug: ZEGERID® (omeprazole) Capsules 20 and 40 mg

Sponsor: Santarus, Inc.

Material Reviewed

Type of Submission: Electronic

Submission Date: April 26, 2005

Receipt Date: April 27, 2005

Filing Date: June 26, 2005

User-fee Goal Date(s): February 26, 2006

Proposed Indication: For short-term treatment of active duodenal ulcer; short-term treatment of active benign gastric ulcer; treatment of heartburn and other symptoms associated with GERD; short-term treatment of erosive esophagitis; and for maintenance of healing of erosive esophagitis.

Other Background Information: This application was submitted on Common Technical Document format. This a non-fee paying 505 (b)(2) application. Santarus, Inc. is the sponsor for NDA 21-636 Zegerid (omeprazole) Oral Powder for Suspension, 20 mg and was approved on June 15, 2004. NDA 21-636 indications are for: short-term treatment of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment of erosive esophagitis; and maintenance of healing of erosive esophagitis. Santarus, Inc. is also the sponsor of NDA 21-706 for Zegerid (omeprazole) Oral Powder for Suspension, 40 mg and was approved on December 21,2004. NDA 21-706 indications are for: short-term treatment of active benign gastric ulcer, and prevention of upper gastrointestinal bleeding in critically ill patients.

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		Cover.pdf
2. Form FDA 356h (original signature)	X		356h.pdf
a. Establishment information	X		356h.pdf, page 3
b. Reference to DMF(s) & Other Applications	X		356h.pdf, page 1
3. User Fee FDA Form 3397	X		Other/userfee.pdf
4. Patent information & certification	X		Other/patinfo.pdf and other/patcer.pdf
5. Debarment certification (Note: Must have a definitive statement)	X		Other/debar.pdf
6. Field Copy Certification	X		Other/fieldcer.pdf
7. Financial Disclosure	X		Other/financial.pdf
8. Comprehensive Index	X		Ndatoc.pdf
9. Pagination	X		Acceptable
10. Summary Volume	X		Summary
11. Review Volumes		X	All electronic
12. Labeling (PI, container, & carton labels)	X		Labeling
a. unannotated PI	X		Labeling/proposed.pdf and labeling/proposed.doc
b. annotated PI	X		Labeling/annotated.pdf
c. immediate container	X		Labeling/carton-contain.pdf
d. carton		X	N/A

e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	Not submitted
13.Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Crt/datasets/datatoc.pdf
14.Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Crf/crftoc.pdf

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

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		Section 2.5.1, pages 3 – 8.
2. Foreign Marketing History		X	N/A
3. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		Summary\23-qos/pdf
b. Nonclinical Pharmacology/Toxicology	X		Summary\24-nonclin-over.pdf
c. Human Pharmacokinetic & Bioavailability	X		Summary\252-over-pharm.pdf
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis	X		Summary\273-sum-eff.pdf and summary\274-sum-safe.pdf
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Summary\255-benrisk.pdf
5. Summary of Safety	X		Summary\274-sum-safe.pdf
6. Summary of Efficacy	X		Summary\273-sum-eff.pdf

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		17-1-4-investigators.pdf

2. Controlled Clinical Studies			N/A
a. Table of all studies			N/A
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)			N/A
c. Optional overall summary & evaluation of data from controlled clinical studies			N/A
3. Integrated Summary of Efficacy (ISE)	X		Summary\273-sum-eff.pdf
4. Integrated Summary of Safety (ISS)	X		Summary\274-sum-safe.pdf
5. Drug Abuse & Overdosage Information			N/A
6. Integrated Summary of Benefits & Risks of the Drug	X		Summary\255-benrisk.pdf
7. Gender/Race/Age Safety & Efficacy Analysis of Studies			N/A

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		Waiver requested in cover letter.
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.)			N/A
a. Proposed unannotated labeling in			

MS WORD	X		Labeling\labeltoc.pdf
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		Other\exclusivity.pdf

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

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

This application is acceptable for filing from a regulatory project management standpoint.

At the filing meeting the RPM will ask if any of the reviewers want foreign labeling, if available. The RPM will ask the sponsor if the product has been marketed in foreign countries.(Sponsor responded on 5/18/05 via email that there is no foreign marketing history for Zegerid.)

Mary M. Lewis
Regulatory Project Manager

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/s/

Mary Lewis
5/25/05 02:01:25 PM
CSO

Mary Lewis
5/25/05 02:03:55 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-849

Santarus, Inc.
Attention: Christine Simmons, PharmD
Vice President, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, California 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: Zegerid® (omeprazole) Capsules 20 mg and 40 mg

Review Priority Classification: Standard (S)

Date of Application: April 26, 2005

Date of Receipt: April 27, 2005

Our Reference Number: NDA 21-849

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 June 26, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 26, 2006.

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Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

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

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Mary M. Lewis
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/

Mary Lewis
5/25/05 09:50:20 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sammie Beam
Division of Medication Errors and Technical Support
HFD-420, Parklawn, Room 6-34

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Division of Gastrointestinal and Coagulation Drug Products,
HFD-180
Mary Lewis, Parklawn 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/18/05		21-849	New NDA labeling and tradename	4/26/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zegerid (omeprazole) Capsules, 20 & 40 mg	Standard	Proton Pump Inhibitor	January 15, 2006

NAME OF FIRM: Santarus

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 21-849 Zegerid (omeprazole) Capsules, 20 and 40 mg was submitted electronically and may be found in the EDR (pathway - N21849, document date: 26 APR 2005 in the Labeling folder). The PDUFA goal date is 2/26/06. Thank you.

SIGNATURE OF REQUESTOR
Mary M. Lewis, Regulatory Project Manager
HFD-180, 301-827-7475

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

Mary Lewis
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising and Communications, HFD-42
Attention: Shannon R. Benedetto, Pharm.D., MBA
Parklawn Room 17B-17

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Mary Lewis, Parklawn 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
05/18/05		21-849	New NDA labeling	4/26/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zegerid (omeprazole) Capsules, 20 & 40 mg	Standard	Proton Pump Inhibitor	January 15, 2006

NAME OF FIRM: Santarus, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 21-849 for Zegerid (omeprazole) Capsules, 20 & 40 mg was submitted electronically and is a 505 (b)(2) application. It may be found in the EDR entitled N021849, Zegerid (omeprazole) Santarus Inc, document date: 26 Apr 2005 N 000 in the Labeling folder. The PDUFA goal date is February 26, 2006. Please review the carton, container and the package insert. Thank you.

SIGNATURE OF REQUESTOR
Mary M. Lewis, Regulatory Project Manager
HFD-180, 301-827-7475

METHOD OF DELIVERY (Check one)
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/s/

Mary Lewis
5/18/05 11:28:38 AM

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MEMORANDUM OF MEETING MINUTES

Meeting Date: October 22, 2004

Time: 1:00 PM

Location: Parklawn Building, Chesapeake Conference Room

Application: IND 69,937 ZEGERID™ (omeprazole) Capsule 20mg and 40mg
IND 65,687 ZEGERID™ (omeprazole) Chewable Tablet, 20mg and 40 mg

Sponsor: Santarus, Inc.

Type of Meeting: Type B, pre-NDA Meeting

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Mary M. Lewis, RN

FDA Attendees and Titles:
Division of Gastrointestinal and Coagulation Drug Products

Joyce Korvick, M.D., M.P.H.	Acting Director
Ruyi He, M.D.	Medical Team Leader
Lolita Lopez, M.D.	Medical Reviewer
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Mary M. Lewis, RN	Regulatory Project Manager

Division of New Drug Chemistry II

Liang Zhou, Ph.D.	Chemistry Team Leader
Marie Kowblansky, Ph.D.	Chemistry Reviewer

External Constituent Attendees and Titles:
Santarus, Inc.

Christine Simmons	Vice President, Regulatory Affairs
Bonnie Hepburn	Senior Vice President, Drug Development
Warren Hall	Senior Vice President, Product Development & Manufacturing
Laura Weston	Director, Analytical Chemistry
Gerald Proehl	President, Chief Executive Officer

Background:

IND 69,937 Omeprazole Immediate-Release Capsule, 20mg and 40mg, submitted June 3, 2004 for indications of ulcers, GERD and erosive esophagitis.

IND 65,687 Omeprazole Chewable Tablet, 20mg and 40mg, submitted August 2, 2002, for treatment of acid-related disorders of the upper gastrointestinal tract.

Santarus, Inc. submitted a meeting request, dated August 6, 2004 and background packages dated September 27, 2004 and October 15, 2004, to the Division of Gastrointestinal and Coagulation Drug products in preparation for today's meeting. The packages included a list of chemistry and clinical questions.

Meeting Objective:

The purpose of the meeting was to obtain the Agency's comments and recommendations with Santarus' proposals for qualifying an alternate capsule shell vendor, qualifying an alternate contract manufacturing site for the chewable tablet and qualifying an alternate supplier of microencapsulated omeprazole for the chewable tablet dosage form. Secondly, to obtain the Agency's comments on the clinical data that the sponsor proposes to provide in the capsule NDA.

Meeting Summary:

Please find below the Agency's responses to the questions submitted in your background packages of September 27, 2004 and October 15, 2004. Our responses are in **bold.**

CMC QUESTIONS

FDA Comment:

General comment regarding the proposed submission of stability data.

Although we generally recommend at least 12 months of stability data at the time of filing, your proposal to submit six months of stability data, followed by the submission of 12-month data during the time that the application is under review, is acceptable as long as the data are received by us no later than 90 days before the PDUFA goal date. However, you should be aware that an expiration period of no longer than 18 months can be granted based on only twelve months of stability data.

1. Does the Agency concur with the capsule vendor qualification proposal?

FDA RESPONSE:

At least three months of real time and accelerated stability data for product manufactured with capsules from the alternate supplier should be submitted at the time of submission. Additional stability data can be submitted at least 90 days prior to the PDUFA goal date.

Alternately, after approval a CBE-0 supplement can be submitted with three months of stability data on one lot.

2. Does the Agency concur with the alternate chewable tablet contract manufacturing site qualification proposal?

FDA RESPONSE:

At least three months of real time and accelerated stability data for product manufactured at the alternate manufacturing site should be submitted at the time of submission. Additional stability data can be submitted at least 90 days prior to the PDUFA goal date.

Alternately, after approval a CBE-0 supplement can be submitted with three months of stability data on one lot.

3. Does the Agency concur with the alternate microencapsulated omeprazole contract manufacturing site qualification proposal?

FDA RESPONSE:

The specifications for microencapsulated omeprazole (by which the material from the two manufacturers will be compared) are inadequate:

- **The impurity limits should be revised to conform to current ICH recommendations**
- **A particle size requirement, based on samples used in clinical trials, should be added**
- **A Loss on Drying specification, based on stability studies, should be added**
- **Appropriate tests to evaluate the comparability of microencapsulation of omeprazole by the two manufacturers (e.g. dissolution) should be added**

The absence of release or stability data at the time of filing for tablets manufactured with microencapsulated omeprazole from the alternate source is not acceptable. At the time of submission, you will need to submit at least three months of accelerated and real-time stability data for tablets manufactured with omeprazole from the alternate source. You can supplement the data with additional stability data no later than 90 days before the PDUFA goal date.

You should also be aware that expiration dating for the finished dosage form will begin at the time the omeprazole is microencapsulated, not the time when the tablets are manufactured. You may, therefore, find it useful to set a limit on the time between microencapsulation and tablet manufacture.

It is acceptable to submit three months accelerated and room temperature stability data for the microencapsulated omeprazole and release data for the drug product manufactured from that material, assuming appropriate specifications have been defined for the microencapsulated omeprazole.

You may find it useful to request separate pre-NDA meetings to discuss the CMC issues involved in your applications.

Three months accelerated and room temperature stability data for the microencapsulated omeprazole and release data for drug product manufactured from that material is acceptable, assuming appropriate specs for microencapsulation have been defined.

CLINICAL QUESTIONS

1. Do the clinical data from the 20-mg capsule PK/PD study provided in Attachment 3 support the proposed 505(b)(2) new drug application for Zegerid™ 20-mg capsules? The capsule would be indicated for the conditions identified in section 3 (Proposed Indications) of this Meeting Information Package. Similar clinical data from the 40-mg capsule PK/PD study will be forwarded to the Agency as soon as it is available prior to the October 22, 2004 meeting.

FDA RESPONSE:

Yes. The PK/PD data appear to support a proposed 505(b)(2) application for the 20 mg capsule.

2. Based on the discussion in Attachment 3 the sponsor believes that there is a sufficient safety database to support Zegerid™ capsule and chewable tablet NDAs. Does the Agency agree with this statement?

FDA RESPONSE:

The safety database for the 20 mg capsule appears sufficient since Zegerid 20mg has been approved by the Agency. However, the 40mg dose is still under review, therefore we cannot comment on this until the review is final.

3. The sponsor believes that the OME-IR(CAP)-C02, 40-mg trial provides sufficient information to support appropriate labeling on the effect of food on the bioavailability of Zegerid™ capsules. Does the Agency agree with this statement?

FDA RESPONSE:

Yes.

Discussion at Meeting:

Sponsor: Does the 40mg food-effect study support 20 mg and 40 mg capsules?

FDA RESPONSE:

Yes.

Additional Issue for Discussion:

The sponsor needs to clarify the difference in antacid amount among the three formulations, and the type of antacid used.

Zegerid powder for suspension=20 meq NaHCO3
Zegerid capsule=13 meq NaHCO3
Zegerid chewable=
antacid)

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/s/

Mary Lewis
11/19/04 01:20:32 PM

Ruyi He
11/19/04 01:26:20 PM

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