

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-850

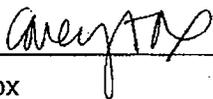
ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

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) Chewable Tablets 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

May 16, 2005
Date

1.3.5.1 PATENT INFORMATION

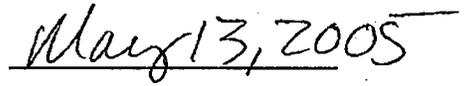
The following patent information is submitted in accordance with 21 CFR §314.53:

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) Chewable Tablets 20 mg and 40 mg, which product is the subject of this application for which approval is being sought.



Joseph A. Mahoney
Patent Counsel



Date

Department of Health and Human Services
Food and Drug Administration

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

**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*

NDA NUMBER

21-850

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

Chewable Tablet

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) 19, 22, 23, 24, 31, 32, 33, 34, 35, 37, 38, 49, 50, 51, 52, 53, 55, and 56. 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

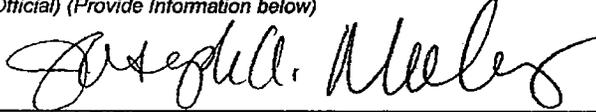
6. Declaration Certification

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



May 12, 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

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

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

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

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/fdahim/fdahim.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

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

**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*

NDA NUMBER

21-850

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

Chewable Tablet

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

6,645,988

b. Issue Date of Patent

11/11/2003

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) 25-28 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

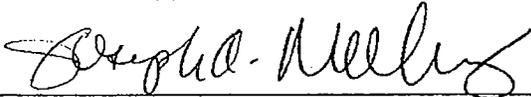
6. Declaration Certification

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



MAY 12, 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

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

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

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

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.
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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

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

**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
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NDA NUMBER

21-850

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

Chewable Tablet

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.

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1. GENERAL

a. United States Patent Number

6,699,885

b. Issue Date of Patent

3/2/2004

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) 1-11, 13-16, 18, and 23-25 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

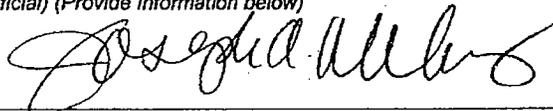
6. Declaration Certification

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



May 12, 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

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

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

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

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/fdahim/fdahim.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 # 21-850

SUPPL # N/A

HFD # 180

Trade Name Zegerid with Magnesium Hydroxide Chewable Tablets, 20 mg and 40 mg

Generic Name omeprazole/sodium bicarbonate/magesium hydroxide

Applicant Name Santarus, Inc.

Approval Date, If Known March 24, 2006

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 21-850) for Zegerid 20 and 40 mg Immediate Release (IR) chewable tablets, filed under 505 (b)(2) provisions, consists of two clinical pharmacology studies, OME-IR (TAB)-C01 and OME-IR (TAB)-C02, plus supportive studies. Study OME-IR (TAB)-C01 evaluated the Pharmacokinetics (PK) and Pharmacodynamics (PD) of omeprazole when Zegerid IR 20 mg chewable tablet was given 1 hour-premeal QD vs Prilosec Delayed Release (DR) 20 mg capsule given QD for 7 days. Study OME-IR (TAB)-C02 evaluated similarly the PK and PD of omeprazole when Zegerid IR 40 mg chewable tablet was given 1 hour-postmeal on Day 8 vs. Zegerid given 1 hour-premeal on Day 7 for both Zegerid IR 20 and 40 mg chewable tablets.

Based on the Agency's bioequivalence (BE) acceptance criteria for PK data obtained from Day 7, Zegerid IR 20 or 40mg chewable tablet is not bioequivalent to Prilosec DR 20 or 40 mg capsule, respectively. Zegerid chewable tablets had higher mean Cmax values than those of Prilosec capsules (30% higher for 40 mg dose and 33% higher for 20 mg dose.) However, Zegerid IR chewable tablets and Prilosec capsules had comparable systemic exposure (AUCs) which met the Agency's BE acceptance criteria. The higher mean Cmax value of Zegerid IR 40 mg chewable tablet obtained from this NDA was found to be comparable to (although 7% higher than) 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?

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:

Name of person completing form: Mary M. Lewis
Title: Regulatory Project Manager
Date: 3/28/06

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

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Joyce Korvick
3/29/2006 03:10:50 PM

1.3.5.3 STATEMENT OF CLAIMED EXCLUSIVITY

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

**APPEARS THIS WAY
ON ORIGINAL**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-850 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 5/25/05 Action Date: 3/26/06

HFD 180 Trade and generic names/dosage form: Zegerid (omeprazole/sodium bicarbonate/magnesium hydroxide) Chewable Tablets, 20 mg, 40 mg

Applicant: Santarus, Inc. Therapeutic Class: 3 and 4

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: 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 21-850
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: for short-term treatment (4-8 weeks) of active, benign gastric 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 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 21-850
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: for 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 21-850
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 #4: 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)?

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 21-850
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 #5: maintenance of healing of erosive esophagitis.

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:

NDA 21-850

Page 10

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 21-850
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)

**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
4/7/2006 11:12:30 AM

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® Chewable Tablets 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:	21-850
Product:	ZEGERID® (omeprazole) Chewable Tablets 20 mg and 40 mg
Sponsor:	Santarus, Inc. 10590 West Ocean Air Drive, Suite 200 San Diego, CA 92130
Indications:	<p>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.</p> <p>Gastric Ulcer. ZEGERID® is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer.</p> <p>Treatment of Gastroesophageal Reflux Disease (GERD) <i>Symptomatic GERD.</i> ZEGERID® Chewable Tablets are indicated for the treatment of heartburn and other symptoms associated with GERD.</p> <p><i>Erosive Esophagitis.</i> ZEGERID® Chewable Tablets are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.</p> <p>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.</p> <p>Maintenance of Healing of Erosive Esophagitis. ZEGERID® Chewable Tablets are indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.</p>
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.

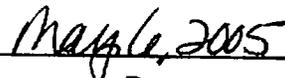
<p>Justification for waiver:</p>	<p>In accordance with 21 CFR §314.55(c), the sponsor requests a full waiver from the requirement that the new drug application contain data on the assessment of safety and effectiveness of ZEGERID® Chewable Tablets for the claimed indications in pediatric patients.</p> <p>The sponsor believes that a waiver of the requirement to conduct clinical studies in pediatric patients is justified by virtue of the following:</p> <ol style="list-style-type: none">1. The physical size of the chewable tablet dosage form. The composition of the ZEGERID® Chewable Tablet formulation requires a tablet 18 mm in diameter and approximately 5½ mm thick. <p>The 18 x 5½ mm chewable tablet is the smallest size that will accommodate the ZEGERID formulation, but this is not an appropriate dosage form for pediatric patients, especially for pediatric patients < 12 years of age. It is unlikely that a tablet of this size will be easily chewed and swallowed by pediatric patients - resulting in low patient compliance. Because of the tablet 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 18 x 5½ mm chewable tablets to be prescribed for pediatric patients < 12 years.</p> <ol style="list-style-type: none">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. <p>Assessments of safety and effectiveness of ZEGERID® Chewable Tablets in pediatric patients would be very unlikely to reveal any meaningful therapeutic benefit over the existing dosage forms appropriate for pediatric patients.</p>
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1.3.3 DEBARMENT CERTIFICATION

Santarus, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this new drug application.



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



Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-850	Efficacy Supplement Type SE-	Supplement Number
Drug: ZEGERID (omeprazole/sodium bicarbonate/magnesium hydroxide) Chewable Tablets, 20mg and 40 mg		Applicant: Santarus, Inc.
RPM: Mary M. Lewis		HFD-180 Phone # 301-796-0941
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 19-810 Prilosec® (omeprazole) Delayed-Release Capsules</p>
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3 and 4
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		03/26/06
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid UF ID number
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input checked="" type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

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

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

() Yes X No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes X No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	N/A
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Admin.Review completed 3/14/06; Appendix B amended 2/28/06.

General Information	
❖ 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)	3/7/06
• Most recent applicant-proposed labeling	3/10/06
• Original applicant-proposed labeling	5/25/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS 1/25/06 DDMAC 2/14/06 M.O. 3/2/06 Phtox 1/31/06 Bioph. 3/7/06 CMC: 3/24/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Prilosec, Prevacid, Nexium
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	05/25/05
• Reviews	DMETS 1/25/06 DDMAC 2/14/06
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes, 1
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes; Fax 3/7/06 to sponsor; 3/20/06 from sponsor.
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ 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 reports (if applicable)	N/A

Summary Appraisal	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	M.O. He 3/15/06 DDD Korvick 3/24/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	3/2/06
❖ 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
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X Sponsor requested a waiver
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	3/7/06
❖ 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	Analytical 1/6/06
CMC	
❖ CMC review(s) (indicate date for each review)	3/24/06
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	N/A
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	(X) Acceptable () Withhold recommendation
❖ Methods validation	(X) N/A () Completed () Requested () Not yet requested
Nonclinical	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1/31/06; IND 65,687 1/12/04.
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

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

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

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

/s/

Mary Lewis
3/30/2006 03:15:53 PM

ulc form

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-850

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

Sponsor: Santarus, Inc.

Material Reviewed

Type of Submission: Electronic

Submission Date: May 25, 2005

Receipt Date: May 26, 2005

Filing Date: July 25, 2005

User-fee Goal Date(s): March 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 is organized using Common Technical Document format and was submitted as 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 approved on June 15, 2004. NDA 21-636 is approved 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 approved on December 21,2004. NDA 21-706 is approved 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	<p>COMMENTS</p> <p>(If paper: list volume & page numbers)</p> <p>(If electronic: list folder & page numbers)</p>
--	---	---	--

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)	X	Crt\datasets\datatoc.pdf

patient data listing or demographic)			
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Crf\crftoc.pdf

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

**APPEARS THIS WAY
ON ORIGINAL**

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 – 9.
2. Foreign Marketing History		X	N/A
3. Summary of Each Technical Section			
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		X	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		Module 5: clinstat/clintoc.pdf; 17.1.4: susp-c07\17-1-4-investigators.pdf

2. Controlled Clinical Studies		
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-safe.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, and Other\waiverrequest.pdf
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.

The RPM will ask the sponsor if the product has been marketed in foreign countries. (Per Charley Davis, via email, it has not.)

Mary M. Lewis
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: 03-21-06

APPLICATION NUMBER: NDA 21-850 Zegerid Chewable Tablets

BETWEEN:

Name: Charles Davis
Phone: 858-314-5753
Representing: Santarus, Inc.

AND

Name: Brian Strongin, CPMS and
Mary Lewis, RPM

SUBJECT: → Site need for inspection for the Magnesium Hydroxide

We called Charley Davis at Santarus on 3/21/06 to inform the sponsor that the Action could be held up because of a need for an inspection of the → site. (The last inspection was 4/2000 per the sponsor; and per Moo Jhong Rhee, ONDQA Branch Chief, these inspections need to be done every 4 years.) Charley stated at that time "the best thing would probably be to withdraw the site", and he would send a withdrawal letter that day after confirming with his team.

SIGNER'S NAME

TITLE

**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
3/27/2006 01:00:24 PM
CSO

Mary Lewis
3/27/2006 01:02:03 PM
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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 _____

_____ 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 _____ (November 14-18, 2005), Form 483 was issued. The objectionable observation and our evaluation are as follows:

-
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, _____ 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

Page 3 of 3 - NDAs 21-849 and 21-850 (Zegerid® Omeprazole
Capsules and Zegerid® Omeprazole Chewable Tablets,
Sponsored by Santarus Inc.

Final Classification:

VAI -

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

/s/

Ray Frankewich
3/24/2006 10:27:08 AM
CHEMIST

Moo-Jhong Rhee
3/24/2006 10:52:31 AM
CHEMIST
Chief, Branch III

A

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-850 Supplement # n/a Efficacy Supplement Type SE- n/a

Trade Name: Zegerid Chewable Tablets
Established Name: omeprazole/sodium bicarbonate/magnesium hydroxide
Strengths: 20 mg/600mg/700mg and 40 mg/600mg/700mg

Applicant: Santarus, Inc.
Agent for Applicant: n/a

Date of Application: May 25, 2005
Date of Receipt: May 26, 2005
Date clock started after UN: n/a
Date of Filing Meeting: July 15, 2005
Filing Date: July 25, 2005
Action Goal Date (optional): User Fee Goal Date: March 26, 2005

Indication(s) requested: For short-term treatment of active duodenal; short-term treatment of active, benign gastric ulcer; treatment of heartburn and other symptoms associated with GERD; short-term treatment of erosive esophagitis; and 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 and 4
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 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

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

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?

Additional comments:

- 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: 65,687
- End-of-Phase 2 Meeting(s)? Date(s) 1/27/2003 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 10/22/2004 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

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 15, 2005

BACKGROUND: This application is a hybrid eNDA 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. Santarus is also the sponsor of NDA 21-849 for Zegerid (omeprazole) Capsules that is in cycle one review period at this time.

(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:

Brian Harvey, M.D., Division Director
Ruyi He, M.D., Medical Officer Team Leader
Lolita Lopez, M.D. Medical Reviewer
Maria Ysern, M.S., Chemistry Reviewer (filling in for Ray Frankewich)
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader
Sushanta Chakder, Ph.D., Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A., Chief Project Management Staff
Mary M. Lewis, RN, Regulatory Project Manager

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

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Lolita Lopez
Secondary Medical:	Ruyi He
Statistical:	(Stella Grosser)
Pharmacology:	Sushanta Chakder
Statistical Pharmacology:	N/A
Chemistry:	Ray Frankewich
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
Regulatory Project Management:	Mary Lewis
Other Consults:	DDMAC: Shannon Benedetto
DMETS: Yes	
DSI: C.T. Viswanathan, Ph.D.	

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: Yes it is an electronic submission.

**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, RN 3/21/06
Regulatory Project Manager, HFD-

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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).

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

1. Does the application reference a listed drug (approved drug)? 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

(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"). This application provides for a change in dosage form, from a delayed-release capsule to an immediate-release chewable tablet.
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): 4,786,505; 4,853,230; 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):

N/A. The applicant is not requesting exclusivity.

- 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
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/s/

Mary Lewis
3/21/2006 12:52:11 PM
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Mary Lewis
3/21/2006 12:54:50 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2006

To: Charles Davis	From: Mary Lewis
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: Revised Post Marketing Commitment statement, NDA 21-850. Please commit to the following Post Marketing Commitment.	

Total no. of pages including cover: 2

Comments:

The dissolution methodology using USP Apparatus — with a speed of — rpm and also using surfactant, —, is relatively unconventional. Please commit to perform a study consisting of expanded dissolution testing using the USP Apparatus 1 — at — rpm (with and without surfactant) for a period of six months after approval. 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: X YES NO

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Attachment

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

/s/

Mary Lewis
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Mary Lewis
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SAN DIEGO, CA 92130
858.314.5700 ▼ FAX 858.314.5701
www.santarus.com

March 20, 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
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Re: NDA 21-850
ZEGERID® (omeprazole/sodium bicarbonate/magnesium hydroxide)
Chewable Tablets 20 mg/600 mg/700 mg and 40 mg/600 mg/700 mg
Amendment 0016
Response to FDA Fax Dated March 20, 2006: Revised Post Marketing
Commitment statement**

Dear Dr. Harvey:

Reference is made to our NDA 21-850 for ZEGERID® (omeprazole 20 mg and 40 mg/sodium bicarbonate 600 mg/magnesium hydroxide 700 mg) Chewable Tablets originally submitted on May 25, 2005. Reference is also made to the fax received on March 20, 2006 in which the FDA asked that we commit to a post marketing dissolution study.

Post Marketing Commitment

We commit to perform a study consisting of expanded dissolution testing using the USP Apparatus 1 (—) at — pm (with and without surfactant) for the first six months of commercial production post approval. Once the study is complete, Santarus will prepare a report and submit it to the Agency for review and re-evaluation of the performance of the dissolution method, with regards to both timepoint and Q value based on the results of these production lots.

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 3.275.00 (Trend Micro Inc). Additionally, our system is automatically updated with the latest virus definition patterns in order to ensure the best protection against viruses.



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 17, 2006

To: Charles Davis	From: Brian Strongin for Mary Lewis
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 21-850: Labeling Comments and Information Requests	

Total no. of pages including cover: 3

Comments:

Please respond to the following comments and information requests regarding NDA 21-850 ASAP. Thanks.

Document to be mailed: YES NO

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

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§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

Brian Strongin
3/17/2006 03:12:17 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2006

To: Charles Davis, Senior Director, Regulatory Affairs	From: Mary Lewis
Company: Santarus, Inc.	Division of Gastroenterology Products
Fax number: 858-314-5788	Fax number: 301-796-9894
Phone number: 858-314-5753	Phone number: 301-796-0941
Subject: Fax Markedup Package Insert, NDA 21-850.	

Total no. of pages including cover: 26

Comments:

Document to be mailed: YES NO

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Attachment



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2006

To: Charles Davis, Senior Director, Regulatory Affairs	From: Mary Lewis
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: Post Marketing Commitment for dissolution testing for NDA 21-850. Please commit to the following Post Marketing Commitment.	

Total no. of pages including cover: 2

Comments: The dissolution methodology using USP Apparatus — with a speed of — rpm and also using surfactant, —, is relatively unconventional. Please commit to perform a study consisting of expanded dissolution testing using the USP Apparatus 1 — at — rpm (with and without surfactant) for a period of six months after approval. During this time, the 60 minute data will be used as the release specification with a Q value of — (NLT — at the S1 level) for 20 mg chewable tablets and a Q value of — (NLT — at the S1 level) for 40 mg chewable tablets. 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 products lots.

Document to be mailed: YES NO

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/s/

Mary Lewis
3/7/2006 12:08:52 PM
CSO

Mary Lewis
3/7/2006 12:12:07 PM
CSO



NDA 21-850

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Charles Davis, RAC
Senior Director, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200
San Diego, CA 92130

Dear Mr. Davis:

Please refer to your May 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid Chewable Tablets (omeprazole/ sodium bicarbonate/magnesium hydroxide) 20 mg and 40 mg.

We are reviewing the Biopharmaceutical and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Amend your drug product stability commitment so that it provides for testing of:
 - The first three commercial-scale batches of each tablet strength;
 - Testing at the ICH Intermediate storage condition (30°C/65% RH) for each commercial-scale batch for at least — The batches of drug product made using omeprazole from — for which stability data have been submitted may be regarded as the first commercial batch.
- Amend the drug product stability specification to provide for the same acceptance criteria and methodology for the Dissolution test that appear in the release Specification. Reference is made to the proposed interim acceptance criteria (and development of new methodology) for the Dissolution test at release, contained in the information request faxed to you on March 7, 2006.

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

3/7/2006 12:43:57 PM



NDA 21-850

INFORMATION REQUEST LETTER

Santarus, Inc.
Attention: Charles Davis, RAC
Senior Director, Regulatory Affairs
10590 West Ocean Air Drive, Suite 200

San Diego, CA 92130

Dear Mr. Davis:

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

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. This request was emailed to you on February 23, 2006 from Mary Lewis. We request a prompt written response in order to continue our evaluation of your NDA.

Provide complete information regarding _____, one of the suppliers of Magnesium Hydroxide _____, including address(es), telephone number(s) of both the manufacturing facility and corporate offices. In addition, provide information regarding the following, if it exists: contact person (name, address and telephone number): CFN number; and inspection history.

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
2/27/2006 09:55:18 AM



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

February 24, 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
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-850
**Zegerid® (omeprazole 20 mg and 40 mg/sodium bicarbonate 600 mg/
magnesium hydroxide 700 mg) Chewable Tablets**
Amendment Number 0008
Supplier Information (Magnesium Hydroxide) and Patent Certification

Dear Dr. Harvey:

Reference is made to NDA 21-850 for Zegerid (omeprazole 20 mg and 40 mg/sodium bicarbonate 600 mg/magnesium hydroxide 700 mg) Chewable Tablets originally submitted on May 25, 2005. Reference is also made to the e-mail communication received on February 23, 2006, requesting information about the supplier of magnesium hydroxide

our supplier of magnesium hydroxide, has provided the following information:

Corporate Office:

Main Contact:

Manufacturing Site:

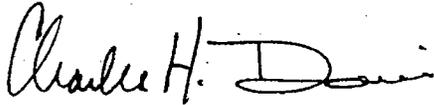
8.

There is no FDA inspectional history at the site in

At this time we are also responding to the telephone request of February 24, 2006 regarding patent certification. We have not received any notification from the patent holders that they intend to sue Santarus with respect to NDA 21-850 for Zegerid Chewable Tablets.

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

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MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Predecisional Agency Information

Date: February 14, 2006

From: Michael Brony, Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Mary Lewis, Division of Gastrointestinal and Coagulation Drug Products

Re: NDA 21-850 Zegerid (omeprazole) Chewable Tablets 20 & 40mg draft label review

DDMAC has no comments on the draft label, draft carton, and draft container labels at this time.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Michael Brony
2/14/2006 12:40:02 PM
CSO

CONSULTATION RESPONSE

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

DATE RECEIVED: December 7, 2005	DESIRED COMPLETION DATE: January 31, 2006	ODS CONSULT #: 05-0127-1 (NDA 21-849)
DOCUMENT DATE: April 26, 2005 (NDA21-849) May 25, 2005 (NDA 21-850)	PDUFA DATE: February 26, 2006 (NDA 21-849) March 26, 2006 (NDA 21-850)	05-0135-1 (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: Zegerid® Omeprazole Capsules 20 mg and 40 mg NDA#: 21-849 Zegerid® Omeprazole Tablets (Chewable) 20 mg and 40 mg NDA#: 21-850	NDA SPONSOR: Santarus, Inc.
--	------------------------------------

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 error¹. 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 databases⁴ 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 conducted⁵. 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 form(s), Established name	Usual adult dose*	Other**
Zegerid	Omeprazole Capsules 20 mg, 40 mg Omeprazole Tablets (Chewable) 20 mg, 40 mg	20 mg – 40 mg once 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 extension 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

Zegerid

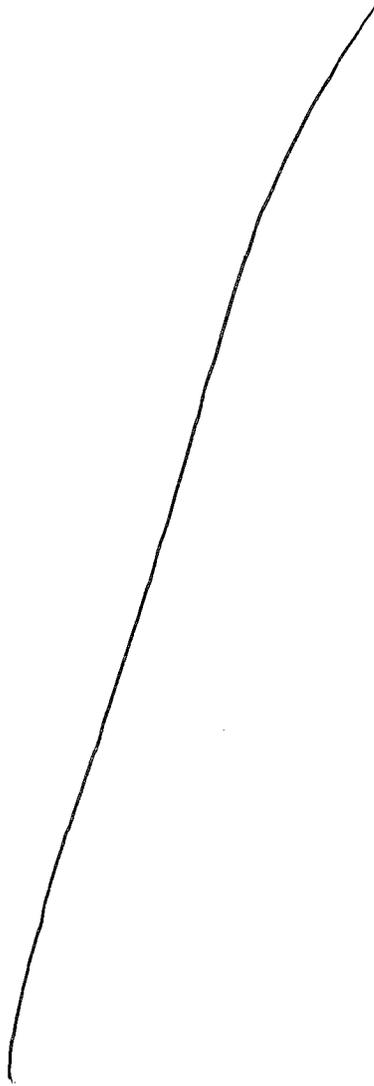
Zestril vs. Zegerid

Zegrid

Zestril

"Zegrid" vs. Zestril

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES



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§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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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

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3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

LEAD

MEMORANDUM

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

DATE: August 25, 2005

TO: Director, Investigations Branch
Kansas City District Office
11630 West 80th Street
Lenexa, KS 66214-3338

FROM: *for* C.T. Viswanathan, Ph.D. *Paul H. Havelmann 8/25/05*
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2005, **High Priority CDER User Fee NDA**, Pre-Approval
Data Validation Inspection, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 21-850
DRUG: Zegerid[®] (Omeprazole) Chewable tablets
SPONSOR: Santarus Inc., San Diego, CA.

This memo requests that you arrange for inspection of the analytical portion of the following bioequivalence study. **Due to the User Fee deadline, this inspection should be completed by December 9, 2005.**

Study: OME-IR(TAB)-C02: "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"

Analytical
Study Number: AA20651-01

Analytical
Site: /

Analytical
Method: LC/MS/MS

Analytical
Investigator: —

Page 2 of 2: NDA 21-850, Zegerid® (Omeprazole) Chewable Tablets

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

Following the identification of the ORA investigator, background material will be forwarded directly. **A member of the Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: Sriram Subramaniam, Ph.D.
(301) 594-1051

cc:

HFD-45/RF

HFD-48/Subramaniam(2)/Himaya/CF

HFD-180/Lewis/NDA 21-850

HER-SW350/Montgomery (please FAX copy to 913-752-2413)

Draft: SS 8/25/05

DSI: 5636; O:\BE\assigns\bio21850a.doc

FACTS 662260



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-850

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 May 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Chewable Tablets, 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 (TAB)-C01 and OME-IR (TAB) 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
8/18/2005 10:04:26 AM



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

July 29, 2005

Brian Harvey, MD, PhD
Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, MD 20857

**Re: ZEGERID® (omeprazole) Chewable Tablets 20 mg and 40 mg
NDA 21-850
Amendment 0002
Documentation of Receipt of Notice to Appropriate Parties of Invalidity or
Noninfringement of Patents in Accordance with 21 CFR 314.52(a) and (c)**

Dear Dr. Harvey:

Please refer to NDA 21-850 for Zegerid® Chewable Tablets 20 mg and 40 mg, submitted on May 25, 2005. Pursuant to 21 CFR Part 314.52(e), Santarus, Inc. is amending this NDA to document receipt of the notice required under 21 CFR 314.52(a). As of July 27, 2005, a return receipt for each notification was confirmed from each person identified under paragraph (a) of this section and the notification met the content requirement under paragraph (c) of this section.

If there are questions about any aspect of this application please contact:

Charles H. Davis, RAC
Senior Director, Regulatory Affairs
Santarus, Inc.
10590 West Ocean Air Drive, Suite 200
Telephone: 858-314-5753
Facsimile: 858-314-5788
Mobile: 949-683-0805
E-mail: cdavis@santarus.com

Sincerely,

Charles H. Davis, RAC
Senior Director, Regulatory Affairs

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FILING COMMUNICATION

NDA21-850

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

Dear Dr. Simmons:

Please refer to your May 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zegerid (omeprazole) Chewable Tabs, 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 July 25, 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:

- Provide one updated specification for the omeprazole that applies throughout the shelf life of the drug product. Acceptance criteria that are part of this specification should be based on actual test data.

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

7/28/05 11:17:29 AM



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

July 25, 2005

Brian Harvey, MD, PhD
Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, MD 20857

**Re: ZEGERID® (omeprazole) Chewable Tablets 20 mg and 40 mg
NDA 21-850
Amendment 0001
Certification of Notification to Appropriate Parties of Invalidity or
Noninfringement of Patents in Accordance with 21 CFR 314.52(a) and (c)**

Dear Dr. Harvey:

Pursuant to 21 CFR Part 314.52(b), Santarus, Inc. is amending this NDA with the following certification. Santarus hereby certifies that as of July 25, 2005, notice has been provided to each person identified under paragraph (a) of this section and the notification met the content requirement under paragraph (c) of this section.

A further amendment will follow upon return receipt for each notification, pursuant to 21 CFR 314.52(e).

If there are questions about any aspect of this application please contact:

Charles H. Davis, RAC
Senior Director, Regulatory Affairs
Santarus, Inc.
10590 West Ocean Air Drive, Suite 200
Telephone: 858-314-5753
Facsimile: 858-314-5788
Mobile: 949-683-0805
E-mail: cdavis@santarus.com

Sincerely,

A handwritten signature in cursive script that reads "Christine Simmons".

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-850

Santarus, Inc.
Attention: Christine Simmons, PharmD
Vice President, Regulatory Affairs and Quality Assurance
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) Chewable Tablets, 20 mg and 40 mg

Review Priority Classification: Standard (S)

Date of Application: May 25, 2005

Date of Receipt: May 26, 2005

Our Reference Number: NDA 21-850

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

Please cite the NDA number listed 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:

Food and Drug Administration
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, 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
6/16/05 11:13:50 AM

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 _____ vendor, qualifying an alternate contract manufacturing site for the chewable tablet and qualifying an alternate supplier of _____ 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



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1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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 NaHCO_3

Zegerid capsule=13 meq NaHCO_3

Zegerid chewable=; NaHCO_3 and MgOH (total of meq antacid)

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/s/

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

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