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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-636

Administrative/Correspondence Reviews



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SAN DIEGO, CALIFORNIA 92130
858.314.5700 ▼ FAX 858.314.5701
www.santarus.com

October 15, 2003

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

N000(c)
NEW CORRESP

**Re: NDA 21-636; Original New Drug Application
Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral
Suspension (OSB-IR) 20 mg
Amendment #001; Certification Santarus notified appropriate parties of invalidity
or noninfringement of patents in accord with 21 CFR 314.52(a) & (c)**

Dear Sir/Madam,

Pursuant to 21 CFR Part 314.52, Santarus, Inc., is submitting an amendment to its original new drug application, NDA 21-636, for Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension (OSB-IR) 20 mg. Santarus hereby certifies that as of October 14, 2003, 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.

We look forward to working with the Agency on this NDA. Please direct any questions on this application to me using the contact information below.

Sincerely,

Christine Simmons, PharmD
Vice President, Regulatory Affairs and Quality Assurance
Cell Phone 858-229-4772
Office Telephone 858-314-5731
Office Fax 858-314-5705
csimmons@santarus.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-636

APPLICANT INFORMATION

NAME OF APPLICANT Santarus, Inc.	DATE OF SUBMISSION 10/15/03
TELEPHONE NO. (Include Area Code) (858) 229-4772	FACSIMILE (FAX) Number (Include Area Code) (858) 314-5705
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 10590 West Ocean Air Drive Suite 200 San Diego, CA 92130-4682	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-636		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Omeprazole	PROPRIETARY NAME (trade name) IF ANY TBD	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Omeprazole	CODE NAME (If any) SAN-05, OSB-IR	
DOSAGE FORM: Powder for Suspension	STRENGTHS: 20 mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

duodenal ulcer, gastroesophageal reflux disorder (GERD), erosive esophagitis, maintenance of healing of erosive esophagitis

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Prilosec</u> Holder of Approved Application <u>Astra Zeneca</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> OTHER <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> EFFICACY SUPPLEMENT
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: <u>N/A</u>
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION

Certification: Santarus notified appropriate parties of invalidity or noninfringement of patents in accord with 21CFR314.52(a) & (c)

PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>N/A</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See the attached document entitled "Establishment Information, Supplement to Form FDA 356h"

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 46,656, OSB-IR; DMF: []
and Type III DMF # []

[] DMF []

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

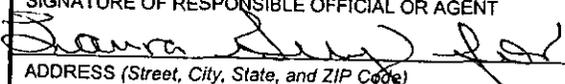
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Christine Simmons, PharmD	DATE: 10/15/03
ADDRESS (Street, City, State, and ZIP Code) 10590 West Ocean Air Drive; Suite #200; San Diego, CA 92130-4682		Telephone Number (858) 229-4772

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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.

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

1.3.1 PATENT INFORMATION

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

US Patent No.	Expiration Date	Type	Patent Owner
5,840,737	July 15, 2016	Method of Use	The Curators of the University of Missouri
6,489,346	July 15, 2016	Composition; Method of Use	The Curators of the University of Missouri

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

Signature: 
Name: Joseph A. Mahoney
Title: Patent Counsel
Date: August 1, 2003

1.3.2 PATENT CERTIFICATIONS

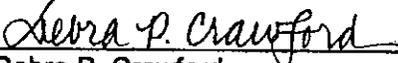
Paragraph II Certification

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

Paragraph IV Certification

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

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



Debra P. Crawford
Vice President and Chief Financial Officer

EXCLUSIVITY SUMMARY FOR NDA # 21-636 SUPPL # N/A

Trade Name unknown Generic Name omeprazole powder for oral suspension

Applicant Name Santarus, Inc. HFD # 180

Approval Date If Known N/A

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES // 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 sponsor conducted 2 bioequivalence studies comparing the PK/PD of their product and Prilosec. The sponsor is relying on the Agency's findings of safety and efficacy from NDA 19-810 for Prilosec.

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 /X/

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 /X/ 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?

No

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

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

YES /___/ NO /X/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES / X / NO / ___ /
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-810 Prilosec
NDA# _____
NDA# _____

2. Combination product. N/A

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

YES / ___ / NO / ___ /

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

NDA# _____
NDA# _____
NDA# _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

1. Does the application contain reports of clinical

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

YES /___/ NO /_X/

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support

the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

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

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

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

Investigation #1	:		
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	
		!	
Investigation #2	:		
IND # _____	YES /___/	!	NO /___/ Explain: _____

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

Investigation #1	:		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	
Investigation #2	:		
YES /___/ Explain _____	!	NO /___/ Explain _____	
_____	!	_____	
_____	!	_____	

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

YES /___/ NO /___/

If yes, explain: _____

Signature Joyce Korvick , M.D., M.P.H.
Title: Deputy Division Director

Date

Form OGD-011347 Revised 05/10/2004

**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
6/30/04 11:04:12 AM
for Dr. Robert Justice

SANTARUS, INC.
CONFIDENTIAL

NDA 21-636
1.3.10 Claimed Exclusivity
Page 1

1.3.10 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/BLA #: 21-636 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: August 15, 2003 Action Date: June 15, 2004

HFD 180 Trade and generic names/dosage form: omeprazole powder for oral suspension

Applicant: Santarus, Inc. Therapeutic Class: 35

Indication(s) previously approved:

1. short-term treatment (4-8 wks) of active duodenal ulcer
2. treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD);
3. short-term treatment(4-8 wks)of erosive esophagitis which has been diagnosed by endoscopy;
4. maintenance of healing of erosive esophagitis.

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

Number of indications for this application(s): 4

Indication #1: short-term treatment (4-8 wks) 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: Ages 2 to 16

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): Within three years of approval date or other reasonable timeframe

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:

Indication #2: 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 X 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: 2 to 16 years of age

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): Within three years of approval date or other reasonable timeframe

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:

Indication #3: short-term treatment (4-8 wks) 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: 2 to 16 years of age

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): Within three years of approval date or other reasonable timeframe

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:

Indication #4: 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 ___ X 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: 2 to 16 years of age

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: 2 to 16 years of age

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): Within three years of approval date or other reasonable timeframe

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}

Susan Daugherty
Regulatory Project Manager

cc: NDA 21-636
HFD-960/ Grace Carmouze

(revised 10-14-03)

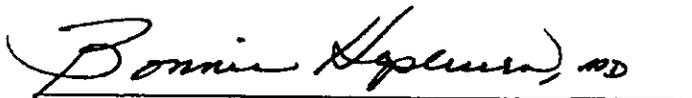
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

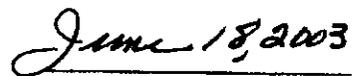
Susan B. Daugherty
6/8/04 09:30:34 AM

1.3.3 Debarment Certification

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



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



Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-636	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: omeprazole powder for oral suspension		Applicant: Santarus, Inc.
RPM: Susan Daugherty		HFD- 180 Phone # (301) 827-7456
Application Type: () 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 19-810 Prilosec [®] (omeprazole) Delayed-Release Capsules
❖ Application Classifications:		
• Review priority		(X) Standard () Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		June 15, 2004
❖ Special programs (indicate all that apply)		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review
❖ User Fee Information		
• User Fee		() Paid
• User Fee waiver		(X) Small business () Public health () Barrier-to-Innovation () Other
• User Fee exception		() Orphan designation () No-fee 505(b)(2) () Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		() Yes (X) No
• This application is on the AIP		() Yes (X) No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		(X) Verified
❖ Patent		
• Information: Verify that patent information was submitted		(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) () I (X) II () III (X) IV 21 CFR 314.50(i)(1) () (ii) () (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		(X) Verified
❖ Exclusivity Summary (approvals only)		In Draft

Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	March 25, 2004
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA In Draft
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) 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)	N/A
• Most recent applicant-proposed labeling	May 18, 2004
• Original applicant-proposed labeling	August 14, 2004
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS December 29, 2003 DMETS May 7, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Prilosec, Prevacid, Nexium, Protonix, Aciphex
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	May 18, 2004
• Reviews	DMETS Review 12-29-04; Clinical Review 1-23-04, 5-11-04; BP 5-18-04; CMC 3-9-04, 4-22-04; P/T 4-25-04
❖ Post-marketing commitments	PENDING
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	(X)
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 25, 2002
• Pre-NDA meeting (indicate date)	March 20, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	October 30, 2001; June 10, 2003
Advisory Committee Meeting	N/A
• Date of Meeting	N/A
• 48-hour alert	N/A

Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	Pending
❖ Clinical review(s) <i>(indicate date for each review)</i>	January 23, 2004; May 11, 2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	(X)
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	May 18, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	March 22, 2004
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	March 9, 2004; April 22, 2004
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	March 9, 2004 (page 6)
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: 11-14-03 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) N/A () Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	April 25, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

MEMORANDUM

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

DATE: 6/14/2004

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

SUBJECT: Director (Deputy) Summary Approval Comments
NDA 21-636

APPLICANT: Santarus, Inc.

DRUG: Zegerid® (omeprazole) Powder for Oral Suspension, 20 mg

DIVISION RECOMMENDATION:

The Division recommends approval of Zegerid® (omeprazole) Powder for Oral Suspension, 20 mg for the following indications:

1. 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.

2. Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

Zegerid is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

Zegerid is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis, which has been diagnosed by endoscopy.

(See CLINICAL PHARMACOLOGY, Clinical Studies.)

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 (e.g. heartburn), additional 4-8 week courses of omeprazole may be considered.

3. Maintenance of Healing of Erosive Esophagitis

Zegerid Powder for Oral Suspension is indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

In addition, Santarus has agreed to the following phase 4 commitments:

I. BACKGROUND:

This is a 505(b)(2) application of a new formulation of the omeprazole product based upon the currently approved prescription omeprazole product, Prilosec. The firm is referencing the Agency's findings of safety and efficacy for clinical and nonclinical studies from NDA 19-810 for Prilosec (Omeprazole) Delayed-Release Capsules. This product is an immediate release powder for oral suspension in water. The product includes sodium bicarbonate, which is an active excipient preventing the degradation of the omeprazole powder by the gastric acid. The sodium bicarbonate is not an active ingredient; that is, it is not intended to treat the medical conditions for which this product is being approved. It is not, therefore, a combination product. The applicant has submitted chemistry and manufacturing information as well as biopharm studies.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

DMETS rejected the proposed tradenames of Rapinex. J This
was communicated to the Santarus who proposed two new tradenames Zegerid and
L 1 The major objection to the name of Rapinex is the potential look-alike
similarities to Regranex. It was felt that the addition of a P to the name would not
address this problem. Further it was noted that IR (immediate release) would not be
acceptable in the tradename. It is not a recognized dosage form. Zegerid is acceptable.
The applicant may choose to pursue Rapinex further before marketing the drug by way of
a supplemental NDA submission.

Santarus requested that the term immediate-release be placed in the established name. The Division consulted with the nomenclature committee and the USP regarding the appropriateness of this terminology in the name. The principle for naming drugs assumes that formulation is immediate release unless otherwise indicated. There is no listing for the term immediate-release in the CDER Data Standards Manual for drug nomenclature (<http://www.fda.gov/cder/dsm/index.htm>). The applicant was concerned that their product not be confused with the currently marketed products and that this be clearly

communicated to the medical profession. The Division pointed out that there was not a safety or efficacy concern in case of confusion regarding these drugs. The dosage and administration were clearly labeled and the safety and efficacy would be the same based upon reliance on pharmacokinetics and pharmacodynamic data and the 505(b)(2) mechanism. The Division further discussed the potential for improper marketing regarding the wording of "immediate-release." Based upon the indications in this approval there is no additional benefit of the omeprazole powder compared to the approved delayed release formulations. Santarus stated ☐

☐ The Division resolved this issue by allowing Santarus to describe the formulation as immediate-release in the body of the label (see labeling review below).

B. Chemistry:

Omeprazole power (the racemic mixture) is supplied in unit dose packets as an immediate release formulation to be constituted with water for oral administration. Each packet contains 20 mg of omeprazole and the following excipients: sodium bicarbonate, sucrose, sucralose, xanthan gum, xylitol, and flavorings.

From a Chemistry standpoint, this product is acceptable.

C. Pharmacology/Toxicology:

No new pre-clinical pharmacology or toxicology data were submitted to this 505(b)(2) application.

From a pre-clinical standpoint, this product is acceptable.

D. Biopharmaceutics:

Santarus submitted 3 clinical pharmacology studies to this NDA. Two study the pharmacokinetic and pharmacodynamic profiles of the 40-mg dose. One study, OSB-IR-C06 studies the 20-mg dose. In this study the comparison of the PK profiles following administration of multiple 20 mg doses of omeprazole powder and Prilosec Delayed Release Capsules indicated that the C_{max} for omeprazole power 20mg was higher (57-60%) than that for the Delayed-Release product. Thus, the two preparations are not bioequivalent, however, the AUCs are similar. The pharmacodynamic results reveal similar profiles for intragastric pH between the two formulations for integrated acidity, mean gastric acid concentration, percent time gastric pH < 4, and mean gastric pH.

A significant food effect on the pharmacokinetics of the omeprazole power formulation was demonstrated. One-hour post-meal, AUC and C_{max} levels of omeprazole were reduced by 24% and 63%, respectively relative to values collected when administered 1 hour pre-meal.

From a biopharmaceutical standpoint, this product is acceptable.

E. Clinical Efficacy/Safety:

No new clinical studies were submitted for this 505(b)(2) application.

The medical reviewers found this application approvable with addition of information in the label regarding the amount of sodium bicarbonate contained in the product. Zegerid contains 1680 mg (20 mEq) of sodium bicarbonate. Zegerid contains 460 mg sodium per dose in the form of sodium bicarbonate. Because it is an active excipient and not a combination product, this information was included in the PRECAUTIONS section of the label and not the chemistry section.

There are no additional safety issues raised by this formulation. The higher C_{max} is not expected to have any clinically meaningful effect on the safety of this formulation because the C_{max} of omeprazole is below that for Prilosec 40 mg, which does not raise any safety concerns.

From a clinical standpoint, this product is acceptable.

F. Pediatrics:

While Prilosec (omeprazole) Delayed-Release Capsules is approved for use in pediatric GERD (symptomatic GERD and erosive esophagitis), the clinical reviewers recommended against including this clinical information until additional pediatric data was collected. This was due to the fact that the active excipient, sodium bicarbonate, may act differently in pediatric patient patients. Therefore, more information is needed regarding the PK/PD parameters in pediatric patients before the current pediatric omeprazole (Prilosec) indications could be extended to the immediate-release powder formulation. For the GERD indications, PK and PD studies would be the basis upon which this request would be evaluated. These studies are outlined in the phase 4 commitments.

III. PHASE 4 COMMITMENTS:

Postmarketing commitments:

- 1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 11 years.
Protocol submission by: December 15, 2004 (6-mos. post-approval)
Study start: July 15, 2005 (1 year post-approval)
Final report submission: July 15, 2007 (3 years post approval)
- 2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.
Protocol submission by: December 15, 2004 (6-mos. post-approval)
Study start: July 15, 2005 (1 year post-approval)
Final report submission: July 15, 2007 (3 years post approval)

IV. LABELING ISSUES:

Name: Currently approved as Zegerid® (omeprazole) Powder for Oral Suspension
Immediate release: is currently in the body of the label only, and is not directly adjacent to the tradename or established name. It is found in the following sections:

DESCRIPTION:

“Zegerid Powder for Oral Suspension is supplied in unit dose packets as an immediate release formulation to be constituted with water for oral administration.”

CLINICAL PHARMACOLOGY:

“Omeprazole is acid labile and thus rapidly degraded by gastric acid. Zegerid Powder for Oral Suspension is an immediate-release formulation that contains sodium bicarbonate to protect omeprazole from acid degradation.”

DOSAGE AND ADMINISTRATION:

Preparation and Administration of Suspension

“Zegerid is supplied as unit dose packets containing an immediate release formulation of omeprazole 20 mg.”

Food Interactions: are described in the pharmacokinetics section and in the Dosage and Administration section:

Preparation and Administration of Suspension

“Zegerid should be taken on an empty stomach 1 hour before a meal.”

Pediatric section: “There are no adequate and well-controlled studies in pediatric patients with Zegerid.”

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/s/

Joyce Korvick
6/15/04 01:22:27 PM
MEDICAL OFFICER

6/14/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

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

Dear Dr. Simmons:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole powder for oral suspension.

We request a letter agreeing to the following post-marketing commitments:

- 1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 11 years.

Protocol submission by: December 15, 2004 (6 mos. post-approval)
 Study start: July 15, 2005 (1 year post-approval)
 Final report submission: July 15, 2007 (3 years post approval)

- 2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.

Protocol submission by: December 15, 2004 (6 mos. post-approval)
 Study start: July 15, 2005 (1 year post-approval)
 Final report submission: July 15, 2007 (3 years post approval)

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
 Director
 Division of Gastrointestinal and
 Coagulation Drug Products
 Office of Drug Evaluation III

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

/s/

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

June 11, 2004

Robert L. Justice, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Parklawn Building Document Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

**Re: NDA 21-636
Amendment Number 0026
Omeprazole Immediate-Release Powder for Oral Suspension (OSB-IR) 20 mg
Post-Marketing Commitments**

Dear Dr. Justice,

Please refer to NDA 21-636 for OSB-IR 20 mg. Santarus is amending NDA 21-636 with the following post-marketing commitments:

1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 2 to 12 years.

Protocol submission by: December 15, 2004 (6 mos. post-approval)
Study start: July 15, 2005 (1 year post-approval)
Final report submission: July 15, 2007 (3 years post approval)

2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 12 to 16 years.

Protocol submission by: December 15, 2004 (6 mos. post-approval)
Study start: July 15, 2005 (1 year post-approval)
Final report submission: July 15, 2007 (3 years post approval)

00717/2007 01130 000143101 SANTARUS
Please direct any questions regarding this amendment to me using the contact information below.

Sincerely,



Christine Simmons, PharmD
Vice President, Regulatory Affairs & Quality Assurance
Santarus, Inc.
Cell Phone: 858-229-4772
Office Fax : 858-314-5788
E-mail: csimmons@santarus.com

Omeprazole Immediate-Release Powder for Oral Suspension

Santarus, Inc.

Final Labeling Submission ~~May 18, 2004~~ ^{June 14, 2004}
Received ~~May 19, 2004~~

June 14, 2004

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

6/10/04

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

Dear Dr. Simmons:

Please refer to your August 14, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole powder for suspension.

We also refer to the meeting between representatives of your firm and the FDA on June 7, 2004. The purpose of the meeting was to discuss the Agency's recommendations to remove "immediate-release" from the established name and not use Rapinex or [] as a proprietary name.

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

If you have any questions, call me at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

Memorandum of Meeting Minutes

Meeting Date: June 7, 2004
Meeting Time: 2:30-4:00 p.m.
Meeting Location: Conference Room 'C', 3rd floor, Parklawn Building
Application Number: 21-636 Omeprazole Powder for Oral Suspension
Type of Meeting: Type A
Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Susan Daugherty, B.S.N.

BETWEEN:

Santarus, Inc. Attendees:

Christine Simmons, Pharm.D, Vice President, Regulatory Affairs and Quality Assurance
Gerald Proehl, President and Chief Executive Officer
Bonnie Hepburn, M.D., Senior Vice President, Drug Development and Chief Medical Officer

AND

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

Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Lolita Lopez, M.D., Medical Reviewer
Sushanta Chakder, Ph.D, Pharmacology Reviewer
Susan Daugherty, B.S.N., Regulatory Project Manager
Monika Houston, Pharm.D, Regulatory Project Manager
Mary Lewis, Consumer Safety Officer

Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

Division of New Drug Chemistry II, HFD-820

Eric Duffy, Ph.D., Division Director
Liang Zhou, Ph.D., Chemistry Team Leader
Marie Kowblansky, Ph.D., Chemistry Reviewer

Division of Medication Errors and Technology Support, HFD-420

Carol Holquist, R.Ph., Division Director
Denise Toyer, Pharm.D., Team Leader
Linda Wisnieski, R.N, Safety Evaluator

PURPOSE: Discuss the Agency's recommendations to remove "immediate-release" from the established name and not use Rapinex or [] as a proprietary name.

BACKGROUND: Santarus, Inc. submitted NDA 21-636 as a 505(b)(2) on August 14, 2003, received August 15, 2003, for Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension for the following indications: Short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; maintenance of healing of erosive esophagitis.

A request for a trade name was not submitted with the NDA; however, proposed trade names were submitted to IND 46,656 on November 15, 2002. In that submission, Santarus proposed "Acitrel" and "Rapinex" as proprietary names for omeprazole sodium bicarbonate immediate-release powder for oral suspension. In a letter dated February 9, 2004, the sponsor was informed that "Acitrel" and "Rapinex" were not recommended as proprietary names due to look alike and sound-alike safety concerns and that additional names should be proposed.

On March 2, 2004, the sponsor submitted an appeal to be able to use Rapinex as a proprietary name and also proposed new names for consideration, including " []", and []. In a letter dated May 19, 2004, the sponsor was notified that "Rapinex", [] were not acceptable due to look-alike safety concerns and that "immediate-release" should be removed from the established name so that it reads "omeprazole powder for oral suspension."

DISCUSSION:

Responses to Questions posed by Santarus.

Immediate Release

In order to avoid mishandling or misuse of our product, Santarus feels very strongly that it is important to communicate to physicians and pharmacists that this product is different from the currently available enteric-coated, oral PPIs. Since labels are intended to communicate, and using the phrase, "immediate release", in the name 1) correctly describes the product, and 2) provides important information to healthcare providers.

1. Does DGCDP continue to be concerned about this issue and if so, what are those specific concerns regarding the inclusion of this phrase in the name?

FDA Response

Yes. It is generally understood that a product is immediate-release UNLESS the labeling indicates otherwise. This is true both within CDER and at USP.

It will not be appropriate to include "immediate-release" in the established name. The addition of "immediate release" (IR) to the trade and established name can be confused with other modifiers currently used for extended-release products (e.g., ER).

Moreover, including the modifier IR with the use of the established name is the reverse of the currently accepted practices for naming product extensions for prescription products. Usually the immediate release dosage formulations do not contain a modifier and the extended-release or delayed-release products do.

As already mentioned by DMETS, although the products have different dosage formulations, the dosing frequency is the same as for all the other PPIs, i.e., once a day. Using the modifier "IR" does not provide any distinguishing safety or dosing information to healthcare providers that would be needed to differentiate the immediate release from the extended release product. Finally, there is no concern with this dosage form regarding altering release characteristics.

2. If the Agency has concerns about using this phrase as proposed, does it have concerns about using the term "Immediate Release" outside the name, but on the principal display panel of the labels and labeling?

FDA Response

Yes, we have concerns with using the term immediate release outside the name on the principal display panel of the labels and labeling. The PK/PD profile characteristics of the product are already described in the CLINICAL PHARMACOLOGY section of the package insert.

Trade Name

Santarus has previously described why it is highly unlikely that [redacted] and Regranex would be dispensed incorrectly by a pharmacist and furthermore why there is not a safety issue even if they were. Santarus also offered to further differentiate the two names from both look-alike and sound-alike perspectives.

3. Has the additional information in this briefing package allayed the Agency's concern?

FDA Response

No.

4. If not: Did? Would the Agency supply a copy of the test prescription of [redacted] so that we can conduct a similar study that would contain a larger sample size of health care participants?

FDA Response

None of the participants in the DMETS RX Studies misinterpreted the sample Rapinex prescription as Regranex. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The Agency will not supply a copy of the test prescription of Rapinex. However, the firm is welcome to repeat the RX Studies on their own or with the help of a consultant. As we noted above there are limitations to the extrapolation of these data when using small sample sizes. We also note that the RX

Studies are only one component used in the risk assessment of a potential proprietary name.

5. What specific safety concerns does the Agency have about the potential confusion between these two products?

FDA Response

The two names possess orthographic similarities when scripted. DMETS has historical postmarketing medication error data that indicates, despite differing product characteristics, if two names look similar when scripted, the potential for confusion leading to medication errors increases. We note that at the point where the patient and/or practitioner identify that the wrong drug has been received or dispensed, the medication error has already occurred.

CONCLUSION:

1. Santarus agreed to remove "immediate-release" from the established name so that it reads "omeprazole powder for oral suspension."

/s/

Minutes Preparer: _____

Susan Daugherty, B.S.N.
Regulatory Project Manager

/s/

Chair Concurrence: _____

Ruyi He, M.D.
Medical Team Leader

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

/s/

Susan B. Daugherty
6/10/04 11:00:55 AM

Ruyi He
6/10/04 11:12:52 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

6/9/04

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

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

Dear Dr. Simmons:

Please refer to your submission dated April 15, 2004, requesting a waiver for pediatric studies for omeprazole powder for oral suspension.

We have reviewed the submission and do not agree that a waiver of pediatric studies in patients aged 2 to —'s justified for omeprazole powder for oral suspension for short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; and maintenance of healing of erosive esophagitis because it does not meet the criteria for a waiver as set forth in the Pediatric Research Equity Act of 2003.

Accordingly, a waiver for pediatric studies for this application is denied under 21 CFR 314.55 at this time. Please submit your pediatric drug development plan.

In addition, studies for ages 2 and under are not required as this drug is not indicated for that population. You may submit a Proposed Pediatric Plan Request if you wish to conduct studies in children under 2 years of age.

If you have questions, please call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Joyce Korvick
6/9/04 12:47:49 PM
for Dr. Robert Justice



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 4, 2004

To: Christine Simmons	From: Susan Daugherty
Company: Santarus, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (858) 314-5705	Fax number: (301) 827-7456
Phone number: (858) 314-5731	Phone number: (301) 827-7456

Subject: Responses to questions for the June 7, 2004 meeting

Total no. of pages including cover: 3

Comments: Attached are the FDA responses to your questions. You have the option of canceling our meeting of **June 7, 2004**, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

Document to be mailed: YES NO

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

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

FDA Responses to Questions posed by Santarus

Immediate Release

In order to avoid mishandling or misuse of our product, Santarus feels very strongly that it is important to communicate to physicians and pharmacists that this product is different from the currently available enteric-coated, oral PPIs. Since labels are intended to communicate, and using the phrase, "immediate release", in the name 1) correctly describes the product, and 2) provides important information to healthcare providers.

1. Does DGCDP continue to be concerned about this issue and if so, what are those specific concerns regarding the inclusion of this phrase in the name?

FDA Response

Yes. It is generally understood that a product is immediate-release UNLESS the labeling indicates otherwise. This is true both within CDER and at USP.

It will not be appropriate to include "immediate-release" in the established name. The addition of "immediate release" (IR) to the trade and established name can be confused with other modifiers currently used for extended-release products (e.g., ER). Moreover, including the modifier IR with the use of the established name is the reverse of the currently accepted practices for naming product extensions for prescription products. Usually the immediate release dosage formulations do not contain a modifier and the extended-release or delayed-release products do.

As already mentioned by DMETS, although the products have different dosage formulations, the dosing frequency is the same as for all the other PPIs, i.e., once a day. Using the modifier "IR" does not provide any distinguishing safety or dosing information to healthcare providers that would be needed to differentiate the immediate release from the extended release product. Finally, there is no concern with this dosage form regarding altering release characteristics.

2. If the Agency has concerns about using this phrase as proposed, does it have concerns about using the term "Immediate Release" outside the name, but on the principal display panel of the labels and labeling?

FDA Response

Yes, we have concerns with using the term immediate release outside the name on the principal display panel of the labels and labeling. The PK/PD profile characteristics of the product are already described in the CLINICAL PHARMACOLOGY section of the package insert.

Trade Name

Santarus has previously described why it is highly unlikely that [redacted] and Regranex would be dispensed incorrectly by a pharmacist and furthermore why there is not a safety issue even if they were. Santarus also offered to further differentiate the two names from both look-alike and sound-alike perspectives.

3. Has the additional information in this briefing package allayed the Agency's concern?

FDA Response

No.

4. If not: Did? Would the Agency supply a copy of the test prescription of [redacted] so that we can conduct a similar study that would contain a larger sample size of health care participants?

FDA Response

None of the participants in the DMETS RX Studies misinterpreted the sample Rapinex prescription as Regranex. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The Agency will not supply a copy of the test prescription of Rapinex. However, the firm is welcome to repeat the RX Studies on their own or with the help of a consultant. As we noted above there are limitations to the extrapolation of these data when using small sample sizes. We also note that the RX Studies are only one component used in the risk assessment of a potential proprietary name.

5. What specific safety concerns does the Agency have about the potential confusion between these two products?

FDA Response

The two names possess orthographic similarities when scripted. DMETS has historical postmarketing medication error data that indicates, despite differing product characteristics, if two names look similar when scripted, the potential for confusion leading to medication errors increases. We note that at the point where the patient and/or practitioner identify that the wrong drug has been received or dispensed, the medication error has already occurred.

CONSULTATION RESPONSE

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

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

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

THROUGH: Susan Daugherty
Project Manager
HFD-180

PRODUCT NAME:
Zegerid
Omeprazole Powder for Oral Suspension 20 mg

NDA SPONSOR:
Santarus, Inc.

NDA#: 21-636

SAFETY EVALUATOR: Denise P. Toyer, PharmD.

RECOMMENDATIONS:

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

/S/

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

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 8, 2004

NDA#: 21-636

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

NDA HOLDER: Santarus, Inc

I. INTRODUCTION:

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

PRODUCT INFORMATION

Zegerid is indicated for use in the following:

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

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

II. RISK ASSESSMENT:

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

A. EXPERT PANEL DISCUSSION

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

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

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

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

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

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

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

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

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

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

C. PRESCRIPTION ANALYSIS STUDIES

I. Methodology:

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

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

Synercid
Zegerid

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

Tegretol
Zegerid

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

Zegerid
Vepesid

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

2. \square \square Independent Name Review

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

Table 2.

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

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

III. RECOMMENDATIONS:

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

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

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

DS

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

APPENDIX A

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

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APPENDIX B

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

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NDA 21-636

omeprazole powder for oral suspension

No Microbiology review needed

Susan DG 6/12/04

Appears This Way
On Original

NDA 21-636

omeprazole powder for oral suspension

No Statistics review needed

 6/2/04

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 21, 2004

To: Christine Simmons	From: Susan Daugherty
Company: Baxter	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (858) 314-5705	Fax number: (301) 443-9285
Phone number: (858) 314-5731	Phone number: (301)-827-7456

Subject: Type A Meeting Request granted

Total no. of pages including cover: 2

Comments: This will confirm the teleconference meeting between Santarus and the FDA to be held on **June 7, 2004, 2:30-4:00 (EDT)**. It will be necessary to send 17 copies of the background package to be received **by May 28, 2004**, with one clearly labeled to Susan Daugherty which will contain (1) a Word 97 diskette* or CD with a list of the firm's attendees, including their titles, and (2) specific questions to be answered at the meeting. These items should be in separate files. The background packages should include purpose, objectives, agenda, your attendees and titles, and questions you propose to ask. These background packages are due 2 weeks prior to the meeting. I am also enclosing a tentative list of attendees from the FDA who will be attending this conference.

*** Please send the diskette under separate cover (not with the background packages) to the attention of Susan Daugherty and mark it confidential.**

Document mailed: • YES NO

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List of Tentative FDA Attendees

Robert Justice M.D., M.S., Division Director

Joyce Korvick M.D., M.P.H.; Deputy Division Director

Ruyi He M.D.; Medical Team Leader

Lolita Lopez M.D.; Medical Officer

Jasti Choudary B.V.Sc.; Supervisory Pharmacologist

Sushanta Chakder, Ph.D.; Pharmacology Reviewer

Eric Duffy, Ph.D., Chemistry Office Director

Liang Zhou Ph.D.; Chemistry Team Leader

Marie Kowblansky, Ph.D.; Chemistry Reviewer

Suresh Doddapaneni Ph.D.; Biopharmaceutics Team Leader

Suliman Al-Fayoumi Ph.D.; Biopharmaceutics Reviewer

Carol Holquist, M.D., DMETS Deputy Division Director

Sammie Beam, Drug Safety Office reviewer

Linda Wisnieski, R.N., Drug Safety Office Reviewer

Denise Toyer, Pharm.D., Drug Safety Office Reviewer

Susan Daugherty; Consumer Safety Officer

Monika Houstoun, Pharm D.; Regulatory Project Manager

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/s/

Susan B. Daugherty
5/25/04 08:18:19 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

TRADENAME REVIEW LETTER

5/19/04

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

Dear Dr. Simmons:

Please refer to your August 14, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole powder for suspension.

We also refer to your submission dated March 2, 2004, containing your tradename appeal for Rapinex and additional proposed tradenames []

Our review of the tradenames and labeling is complete, and we have the following comments:

A. Tradename

You have not submitted persuasive evidence to diminish our concerns with potential confusion between Rapinex and Regranex. We do not recommend the use of Rapinex, [] for proprietary names.

B. Labeling

1. Delete the phrase "Immediate-Release" and revise the established name to read: "Omeprazole Powder for Oral Suspension".
2. We note that you have submitted an NDA for the 40 mg strength and we recommend that you consider implementing a method to differentiate between the two strengths, such as expressing the strength with a contrasting color, boxing or some other means.
3. We acknowledge your statement in the submission dated March 22, 2004, that you will obtain data concerning the child-resistant properties of the proposed packaging as soon as it is available.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If

you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

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

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/s/

Julieann DuBeau
5/19/04 01:39:15 PM

26 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-29-03

5-7-04

3/25/04

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-636

Trade Name: Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension
Generic Name: Omeprazole
Strengths: 20 mg

Applicant: Santarus, Inc.

Date of Application: August 14, 2003
Date of Receipt: August 15, 2003
Date clock started after UN:
Date of Filing Meeting: October 1, 2003
Filing Date: October 14, 2003
Action Goal Date (optional): May 11, 2003

User Fee Goal Date: June 15, 2003

Indication(s) requested: Short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; maintenance of healing of erosive esophagitis.

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA X
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid _____ Waived (e.g., small business, public health) X
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # N/A
Clinical data? YES _____ NO, Referenced to NDA # 19-810

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?
 YES NO

If yes, explain:
NDA 19-810 has Waxman-Hatch exclusivity (code M-19) until June 12, 2005 and pediatric exclusivity until January 12, 2006.

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)]?
 N/A YES NO

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 N/A 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 certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

The entire application was submitted electronically.

Additional comments: Those forms requiring an original signature were submitted in paper.

- If in Common Technical Document format, does it follow the guidance? N/A YES NO
 With the following exceptions:
 - A. **Sections 2.5.2 Overview of Biopharmaceutics and 2.5.3 Overview of Clinical Pharmacology have been combined into one section, 2.5.2 Overview of Pharmacokinetic and Pharmacodynamic Data**
 - The Overview of Efficacy becomes Section 2.5.3 instead of Section 2.5.4
 - The Overview Analysis of Safety becomes Section 2.5.4 instead of Section 2.5.5
 - The Benefits and Risks Conclusions becomes Section 2.5.5 instead of Section 2.5.6
 - The Literature References becomes 2.5.6 instead of Section 2.5.7
 - B. **Section 2.7.1 Summary of the Biopharmaceutic Studies and Associated Analytical Methods has been renamed "Summary of the Pharmacokinetic Data and Associated Analytic Methods"**
 - Section 2.7.2 Summary of Clinical Pharmacology Studies has been renamed "Summary of Pharmacodynamic Data"
- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information included with authorized signature? 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 must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix _____." Applicant may not use wording such as "To the best of my knowledge"

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

Refer to 21 CFR 314.101(d) for Filing Requirements

- 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/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
YES
- List referenced IND numbers: IND 46,656
- End-of-Phase 2 Meeting(s)? Date(s) 3/25/02 NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 3/20/03 & 6/10/03 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO
 Requested that we consult further into process.
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO
 Trade name not submitted.
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

<u>N/A</u>	YES	NO
------------	-----	----

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?

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	<u>N/A</u>	NO
-----	------------	----

Chemistry

- Did applicant request categorical exclusion for environmental assessment?

<u>YES</u>	NO
------------	----
- If no, did applicant submit a complete environmental assessment?

YES	NO
-----	----
- If EA submitted, consulted to Nancy Sager (HFD-357)?

YES	NO
-----	----
- Establishment Evaluation Request (EER) submitted to DMPQ?

<u>YES</u>	NO
------------	----
- If parenteral product, consulted to Microbiology Team (HFD-805)?

YES	<u>N/A</u>	NO
-----	------------	----

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: NDA 19-810 Prilosec (omeprazole) Delayed-Release Capsule 20 mg

- 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 delayed-release capsules to immediate-release powder for oral suspension.

- 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.)

YES	<u>NO</u>
-----	-----------
- 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 314.101(d)(9).

YES	<u>NO</u>
-----	-----------

- 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 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

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

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.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(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. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

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

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

- Did the applicant:

- Identify which parts of the application rely on information 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

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A
 - Certification that each 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.

YES, IND # _____ NO
 - OR
A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?
Kim Colangelo notified via e-mail. She will notify HFD-007.

YES NO

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/s/

Susan B. Daugherty
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CSO

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

MARCh 22, 2004



NDA 21-636

DISCIPLINE REVIEW LETTER

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

3-16-04

Dear Dr. Simmons:

Please refer to your August 14, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole immediate-release powder for oral suspension.

We also refer to your submission dated February 19, 2004.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. The drug substance has three sets of specification limits for individual impurities:
 Please update the impurity specifications to one set of consistent specifications that conform to current FDA guidelines. In this connection, please be reminded that official compendia are defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)), which currently does not include the European Pharmacopoeia. Consequently, if a European Pharmacopoeial method is to be used, a copy of the method with validation data should be submitted in the application.
2. Please include: testing in the drug substance specifications. The specified limits should take into account current guidelines and the manufacturing history of the drug substance.
3. Since omeprazole is a racemic mixture, should be added to the list of release specifications.
4. Drug Master File (DMF) which has been reviewed in connection with this application, is deficient. An information request letter itemizing the deficiencies was issued to the DMF-holder on December 22, 2003.

5. [] should be included in the drug product release and stability specifications, until a manufacturing history has been established for the product.
6. The description of commercial-scale batches contain [] Please explain what these represent. If these are [] for the purpose of [] their composition should be identified. 7
7. [] is reported as a relative standard deviation value in the batch analysis results, and as a single average omeprazole value in the stability tabulations. Please clarify this.
8. Analysis of the three commercial-scale batches reveals that between [] of the omeprazole is removed from the packet, [] Consequently, [] is not appropriate and should be eliminated from the manufacturing process.
9. Please make the following changes to your package insert:
 - a. In the **DESCRIPTION** section, a reference should be made to the fact that omeprazole is a racemic mixture of two enantiomers
 - b. For oral dosage forms, the regulations do not require listing the amounts of each excipient on the label. Listing the amount of sodium bicarbonate on the label, and not the amounts of the other excipients, creates the impression that the sodium bicarbonate is an active ingredient in the formulation. You may choose either to list the quantities of all excipients on the label, or not to list the quantities for any of them.
 - c. Please revise your storage statement to read: "Store at 25°C (68°F–77°F); excursions permitted to 15–30 °C (59–86°F) [see **USP Controlled Room Temperature**]."
10. A list of all product components should be included on the packet label.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

NDA 21-636

Page 3

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

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

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/s/

Liang Zhou
3/16/04 04:50:01 PM



NDA 21-636

INFORMATION REQUEST LETTER

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

2-26-04

Dear Dr. Simmons:

Please refer to your August 14, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole immediate-release powder for suspension.

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

1. The drug substance has three sets of specification limits for individual impurities:
 Please update the impurity specifications to one set of consistent specifications that conform to current FDA guidelines. In addition, please note that official compendia are defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)), which currently does not include the European Pharmacopoeia. Consequently, if a European Pharmacopoeial method is to be used, a copy of the method with validation data should be submitted to the application.
2. Although the drug substance is tested there are no official limits Please include as part of the drug substance specifications. The specified limits should take into account current guidelines and manufacturing history of the drug substance.
3. Since omeprazole is a racemic mixture, should be added to the list of release specifications.

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

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

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/s/

Julieann DuBeau
2/26/04 08:09:57 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 26, 2004

To: Christine Simmons	From: Susan Daugherty
Company: Santarus, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (858) 314-5701	Fax number: (301) 443-9285
Phone number: (858) 314-5731	Phone number: (301) 827-7456
Subject: IR letter	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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NDA 21-636

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

Dear Dr. Simmons:

We received your February 13, 2004, correspondence on February 18, 2004, requesting a meeting to discuss your proposed tradename. We considered your request and conclude that the request does not contain adequate information to grant the meeting at this time. Specifically, you failed to provide questions necessary to determine the utility of the meeting and to identify Agency staff required to discuss the proposed agenda items, as indicated in the *Guidance for Industry Formal Meetings With Sponsors and Applicants for PDUFA Products*.

We encourage you to submit an appeal regarding the use of Rapinex as the tradename for your product with supporting documentation and additional proprietary names for consideration.

If you disagree with our decision regarding your meeting request, you may discuss the matter with Susan Daugherty, Regulatory Project Manager, at (301) 827-7456. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fml.htm>.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
2/26/04 03:56:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-636

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

2-26-04

Dear Dr. Simmons:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole immediate-release powder for suspension.

We also refer to your January 15, 2004, submission containing your responses to the filing letter dated October 23, 2003.

We have reviewed the referenced material and recommend that you organize the **CLINICAL PHARMACOLOGY** section of the label as follows:

1. Pharmacokinetics
2. Absorption
3. Distribution
4. Metabolism
5. Excretion
6. Special Populations
7. Geriatric
8. Gender
9. Hepatic insufficiency
10. Renal insufficiency
11. Drug-drug interactions

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
2/26/04 03:14:28 PM
for Dr. Robert Justice



NDA 21-636

DISCIPLINE REVIEW LETTER

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

2/9/04

Dear Dr. Simmons:

Please refer to your August 14, 2003, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for omeprazole immediate-release powder for suspension. We also refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for omeprazole immediate-release powder for suspension.

Our review of the tradenames and labeling submitted November 15, 2002, under IND 46,656 is complete, and we have the following comments:

A. Tradename

We do not recommend use of the proposed proprietary names, Acitrel or Rapinex. The names identified have sound-alike and look-alike similarities to Acitrel are Acthrel and Accupril. The name identified to have sound-alike and look-alike similarity to Rapinex is Regranex. Please consider proposing an alternate proprietary name and submitting it to NDA 21-636.

B. Labeling

Since the labels and labeling were submitted in black and white with only the company logo in color, please note that the Agency has not evaluated and commented on the use of colors, color fonts and/or graphics.

1. General

- a. Revise the established name to read: "Omeprazole Powder for Oral Suspension" throughout the labeling.

2. Carton Labeling (Trade Packet)

- a. Relocate the net quantity statement so that it does not appear in close proximity to the strength. Additionally, revise to read: "Contains 30 single dose packets. Each packet contains 20 mg of Omeprazole."

b. Your proposed carton of 30 packets appears to be packaging. Indicate whether the carton is child-resistant.

3. Carton Labeling (Professional Sample)

a. Your proposed carton of 30 packets appears to be packaging. Indicate whether the carton is child-resistant.

b. Delete the word — from the descriptor It is unclear what a unit represents.

c. Revise the net quantity to read: "Contains 5 single dose packets. Each packet contains 20 mg of Omeprazole."

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}.

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

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

/s/

Julieann DuBeau
2/9/04 11:06:07 AM



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

January 7, 2004

Robert L. Justice, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Parklawn Building Document Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

RECEIVED
JAN 08 2004
FDR/CDER

DUPLICATE

N 000 SU.

Re: NDA 21-636
Amendment Number 004
Omeprazole Immediate-Release Powder for Oral Suspension (OSB-IR) 20 mg
120-Day Safety Update

Dear Dr. Justice,

No new safety information has been obtained by Santarus with regard to Omeprazole Immediate-Release Powder for Oral Suspension 20 mg.

Please direct any questions regarding this amendment to me using the contact information below.

Sincerely,

Christine Simmons, PharmD
Vice President, Regulatory Affairs & Quality Assurance
Santarus, Inc.
Cell Phone: 858-229-4772
Office Fax: 858-314-5705
E-mail: csimmons@santarus.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
21-636

APPLICANT INFORMATION

NAME OF APPLICANT Santarus, Inc	DATE OF SUBMISSION January 07, 2004
TELEPHONE NO. (Include Area Code) (858) 229-4772	FACSIMILE (FAX) Number (Include Area Code) (858) 314-5705
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 10590 West Ocean Air Drive Suite 200 San Diego, CA 92130-4682	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-636		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Omeprazole	PROPRIETARY NAME (trade name) IF ANY Rapinex	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Omeprazole	CODE NAME (If any) SAN-05, OSB-IR	
DOSAGE FORM: Immediate-Release Powder for Oral Suspension	STRENGTHS: 20 mg	ROUTE OF ADMINISTRATION: Oral

PROPOSED INDICATION(S) FOR USE:

Gastric ulcer, gastroesophageal reflux disorder (GERD), erosive esophagitis, maintenance of healing of erosive esophagitis

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>Prilosec</u> Holder of Approved Application <u>Astra Zeneca</u>
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: <u>N/A</u>
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION 120-Day Safety Update
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>N/A</u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See original new drug application dated August 14, 2003.

References (List related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

46,656, OSB-IR; DMF # <u>E</u>	<u>1</u> DMF # <u>C</u>	<u>1</u>
type III DMF #: <u>E</u>		<u>1</u>

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(f); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input checked="" type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

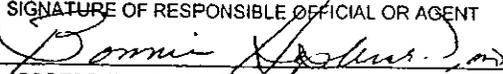
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Bonnie Hepburn, MD	DATE: January 07, 2004
ADDRESS (Street, City, State, and ZIP Code) 10590 West Ocean Air Drive, Suite #200; San Diego, CA 92130-4682		Telephone Number (858) 229-4772

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-636

16-23-03

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 August 15, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Immediate-Release Powder for Oral Suspension.

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 October 1, 2003, in accordance with 21 CFR 314.101(a).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

1. Submit labeling in the format specified under 21 CFR 201.57.
2. [] of stability data were submitted with the application. Since expiration dating will be based on real time stability data, submit additional stability data, no later than six months from the date when your application was submitted.
3. Provide information as to whether your proposed drug substance name, omeprazole sodium bicarbonate, is a USAN name. The name omeprazole powder for oral solution would be a more appropriate drug substance name, since no claim is being made for sodium bicarbonate as an active ingredient.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-636

Page 2

If you have any questions, call Susan Daugherty, Consumer Safety Officer, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
10/23/03 06:01:28 PM

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 1, 2003
Time: 1:00-2:30 pm
Location: Conference Room 6B-45, Parklawn Building

Application: NDA 21-636
Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension

Type of Meeting: 45-Day Filing Meeting

Meeting Chair: Dr. Robert Justice

Meeting Recorder: Susan Daugherty

Attendees:

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

Robert Justice, M.D., M.S., Division Director
Joyce Korvick, M.D., M.P.H., Division Deputy Director
Gary Della'Zanna, D.O., Acting Medical Team Leader, Gastrointestinal Drug Products
Lolita Lopez, M.D., Medical Reviewer
Jasti Choudary, Ph.D., Pharmacology Team Leader
Sushanta Chakder, Ph.D., Pharmacology Reviewer
Liang Zhou., Chemistry Team Leader
Marie Kowblansky, Ph.D, Chemistry Reviewer
Susan Daugherty, B.S.N., Regulatory Project Manager
Paul E. Levine, Jr., R.Ph, J.D. Regulatory Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

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

Division of Biometrics II (HFD-715)

Wen-Jen Chen, Ph.D., Statistics Reviewer

Division of Scientific Investigations (HFD-46)

Khairy Malek M.D., Medical Officer

Office of Pharmaceutical Science (HFD-604)

Don Hare, R.Ph, Consumer Safety Officer
Division of Drug Marketing, Advertising, and Communications (HFD-42)

Laura Pincock, PharmD, Regulatory Review Officer

Background:

Santarus, Inc. submitted NDA 21-636 on August 14, 2003, received August 15, 2003, for Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension for the following indications: Short-term treatment (4-8 wks) of active duodenal ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term treatment (4-8 wks) of erosive esophagitis which has been diagnosed by endoscopy; maintenance of healing of erosive esophagitis.

Meeting Objective:

To determine the fileability of this application.

Discussion Points:

I. Discipline Reports

1. Administrative

- a. Filing Issues: None
- b. Information Requests: None

2. Clinical

- a. Filing Issues: None
- b. Information Requests: None

3. Statistics

- a. Filing Issues: None
- b. Information Requests: None

4. Pharm/Tox

- a. Filing Issues: None
- b. Information Requests:

5. Chemistry\Manufacturing\Controls (CMC)

- a. Filing Issues: None
- b. Information Requests:
 - Dr. Kowblansky requested that the sponsor be notified that the expiration date will be based on submitted stability data. [stability data was submitted. Further stability data should be submitted as soon as possible and no later than 6 months into the review.

6. Biopharmaceutics

- a. Filing Issues: None

b. Information Requests:

- Dr. Doddapaneni requested that the firm submit labeling in the format specified in 21 CFR 201.57.
- Dr. Doddapaneni also requested that DSI be consulted to perform a study inspection.

II. Is Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension a combination product?

In a pre-NDA teleconference on June 10, 2003, the Agency requested that the firm address the reason why the combination drug rule does not apply to Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension. The firm's NDA submission provided the following explanation in their NDA submission:

"At a meeting with Santarus on January 27, 2003, to discuss C J the Agency's chemistry reviewer stated that a reviewing committee had reached the conclusion that the primary role of the antacid in this formulation was to protect the omeprazole from acid degradation, rendering an enteric coating unnecessary for this purpose. This role was not considered sufficient to characterize the antacid(s) as an active ingredient and the **omeprazole antacid formulation would not be considered a combination drug** unless a specific claim regarding the therapeutic effect of the antacid was to be made. All of the targeted indications discussed below require continuous suppression of gastric acid for periods of 4 to 8 weeks or more, and no claim regarding a therapeutic effect of sodium bicarbonate will be made."

Since no therapeutic claim is being made for the sodium bicarbonate component of this drug, it will not be considered a combination product. Don Hare recommended that sodium bicarbonate be omitted from the drug name for the purpose of listing it in the Orange Book. In addition, Mr. Hare suggested listing this product in a special section of the Orange Book to indicate generics must contain the same ingredients.

Conclusions:

1. It was determined that the application would be filed.
2. The application is appropriately submitted as a 505(b)(2). The firm is referencing the Agency's findings of safety and efficacy for clinical and nonclinical studies from NDA 19-810 for Prilosec (omeprazole) Delayed-Release Capsules.
3. The Project Manager will issue a 74-day Filing letter to the firm to convey the information requests from Biopharmaceutics and CMC as indicated above.
4. It was agreed that there will be regular team meetings as outlined in the "Omeprazole Sodium Bicarbonate Immediate-Release Powder for Oral Suspension, NDA 21-636 Review Plan" (see attached).
5. The Project Manager will issue a DSI consult for a study inspection.

NDA 21-636
Filing Meeting Minutes 10/01/03
Page 4

Minutes Preparer: Susan Daugherty

Attachment: Review Timeline

Drafted: SD 10/03/03
Filename: N21-636 Filing Meeting Minutes.doc

FILING MEETING

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Susan B. Daugherty
3/25/04 04:22:35 PM

Omeprazole Immediate-Release Powder for Oral Suspension

Santarus, Inc.

Original Submission August 14, 2003

Received August 15, 2003

Appears This Way
On Original

CTD Components	Item	NDA Folder\Filename
Labeling Folder - Prescribing Information		
1.4 Prescribing Information - Table of Contents	2	labeling\labeltoc.pdf
1.4.1 Proposed Labeling Text	2	labeling\proposed.pdf
1.4.2 Carton Label 20 mg (Quantity 30)	2	labeling\carton2030.pdf
1.4.3 Sample Carton 20 mg (Quantity 5)		labeling\carton205.pdf
1.4.4 Trade Packet 20 mg		labeling\tradepacket20.pdf
1.4.5 Sample Packet 20 mg (Single)		labeling\samplepacket20.pdf
1.5 Proposed Annotated Labeling NOTE: This document includes a comparison to Prilosec labeling.	2	summary\annotated.pdf
1.6 Final Printed Package Insert	2	To be provided when finalized

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On Original

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF MEETING MINUTES

Meeting Date: June 10, 2003

Time: 12:00 PM

Location: Parklawn Building, 3rd Floor, Conference Room "L"

Application: IND 46,656

Type of Meeting: Type B

Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D.

Meeting Recorder: Melissa Furness, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., M.S.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical (GI) Team Leader
Ali Al-Hakim, Ph.D.	Chemistry Reviewer
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Tom Permutt, Ph.D.	Statistics Team Leader
Don Hare, R.Ph.	Generic Drugs
Melissa Furness, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Santarus, Inc.

Bonnie Hepburn, M.D.	VP, Drug Development
C. Simmons, Pharm.D.	VP, Regulatory Affairs & QA
Gerald Proehl	President & CEO
┌	Consultant ┌
└	└

Background:

The purpose of this meeting is to continue discussion and to provide clarification regarding the sponsor's upcoming NDA submissions.

Discussion Points:

Please find below our responses to the questions submitted in your May 13, 2003 Meeting Background Package. Our responses are in **bold**.

1. Santarus believes that the data contained in this pre-meeting package and planned for inclusion in the NDA scheduled for submission in July, adequately support the safety and efficacy of OSB-IR. Does the Agency have any issues or questions regarding the proposed content of the 505(b)(2) NDA 21-636, particularly with regard to the difference in C_{max} values for the two products?

The sponsor should provide clinical data in support of the safety of the proposed product (OSB-IR) (20 mg) given the observed 50% increase in C_{max} relative to that of Prilosec (20 mg).

Your proposal for 20 mg seems acceptable to us for all of the applicable indications (GU, DU, Symptoms of GERD, erosive esophagitis, maintenance and healing of erosive esophagitis).

Please submit your justification to us for your differences in C_{max} .

For the 40 mg, we would like to see a safety study with patients for the duration of treatment of the approved indication (GU).

- 2.

[

]

[

]

3. As above, Santarus seeks guidance with regard to this submission.

Depending on the results of the PK studies, safety and efficacy studies may be required.

4. As with OSB-IR, the safety of OAC-IR will supported by "bridging" PK/PD trials comparing OAC-IR to Prilosec and by additional safety data collected in the OAC-IR Phase 3 trials. Does the Agency have any issues or questions regarding the proposed content of this 505(b)(2) NDA?

See answer to question #3.

FDA Additional Comments:

- **Please remember to address why the combination drug rule does not apply.**

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/s/

Melissa Furness
7/10/03 09:28:05 AM

Hugo Gallo Torres
7/10/03 09:57:39 AM



Christine Simmons, Pharm.D.
Santarus, Inc.
10590 West Ocean Air Drive
Suite 200
San Diego, CA 92130-4682

Food and Drug Administration
Rockville MD 20867

MAY 8 2003

RE: Santarus, Inc., Small Business Waiver Request 2003.036 for Omeprazole Sodium Bicarbonate — Immediate-Release Powder for Suspension, NDA 21-636

Dear Dr. Simmons:

This responds to your March 7, 2003, letter requesting a waiver of the human drug application fee for the new drug application (NDA) for omeprazole sodium bicarbonate — immediate-release powder for suspension, under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.036). For the reasons described below, the Food and Drug Administration (FDA) grants Santarus, Inc.'s (Santarus's) request for a small business waiver of the application fee for NDA 21-636 for omeprazole sodium bicarbonate — immediate-release powder for suspension.

According to your waiver request, Santarus is a small business with — employees and no affiliates. You note that NDA 21-636 will be Santarus's first application submitted to FDA for review under section 505(b) of the Act. You anticipate submission of NDA 21-636 in May 2003.

Under section 736(d)(3)(B) of the Act,² a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate³ submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug-application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Santarus's request for a small business waiver for NDA 21-636 for omeprazole sodium bicarbonate is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated April 7, 2003, that Santarus has fewer than 500 employees. Santarus does not have any affiliates.

Second, according to FDA records, the marketing application for omeprazole sodium bicarbonate, NDA 21-636, is the first human drug application, within the meaning of the Act, to

¹ 21 U.S.C. 379h(d)(1)(D).

² 21 U.S.C. 379h(d)(3)(B).

³ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

be submitted to FDA by Santarus or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-636 is granted, provided that FDA receives the marketing application for omeprazole sodium bicarbonate no later than April 7, 2004, 1 year after the effective date of the size determination made by SBA. Please include a copy of this letter with your application.

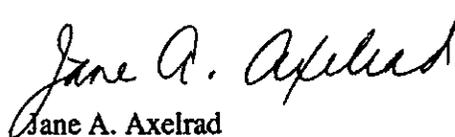
If FDA refuses to file the application or Santarus withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Santarus should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for NDA 21-636.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,



Jane A. Axelrad

Associate Director for Policy
Center for Drug Evaluation and Research

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

MEMORANDUM OF TELECON

EOP 2

DATE: March 25, 2002

APPLICATION NUMBER: IND 46,656

Omeprazole sodium bicarbonate - immediate release, powder for suspension (OSB-IR (PWD

BETWEEN:

Santarus, Inc.

- Robert Bagin, Ph.D., Director, Biostatistics and Data Management
- Bonnie Hepburn, M.D., Vice President, Drug Development
- William Frank, M.D., Vice President, Clinical Affairs
- Debra Gessner, Director, Regulatory Affairs & Quality Assurance
- Christine Simmons, Vice President, Regulatory Affairs & Quality Assurance
- [] Consultant

AND

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

- Joyce Korvick, M.D., Deputy Director
- Hugo Gallo-Torres, M.D., Ph.D., GI Medical Team Leader
- Robert Prizont, M.D., Medical Officer
- Milton Fan, Ph.D., Biostatistics Reviewer
- Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer
- Maria R. Walsh, M.S., Regulatory Project Manager

Background: Santarus, Inc. submitted a proposed [

Teleconference Summary:

The sponsor's list of questions [

]

]

6 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

Discussion:

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Miscellaneous Issue:

Santarus, Inc. also plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study comparing OSB-IR to the listed drug product, Prilosec (omeprazole) Delayed-Release Capsules. An outline of this study, dated February 4, 2002, was submitted to IND 46,656. In a separate teleconference earlier today between Ms. Maria Walsh and Ms. Christine Simmons, Ms. Walsh conveyed the following FDA responses to the sponsor's questions regarding the proposed study:

A. Is it acceptable to the Agency that the test drugs in the proposed PK/PD trial be administered to fasted subjects, one hour before meals?

FDA Response: It is acceptable that the proposed PK/PD study be conducted under fasting conditions.

B. Does the Agency agree that there should be no requirement to study OSB-IR delivered concurrently with food?

FDA Response: The sponsor should evaluate the effect of food on the pharmacokinetics of OSB-IR.

At today's teleconference, the sponsor asked the following additional question regarding the proposed PK/PD study:

C. Is it acceptable to enroll 12 patients in the study?

FDA Response: The study should include a minimum of 12 evaluable subjects.

Because of time constraints, several of the sponsor's questions were not discussed at this teleconference. FDA recommended the sponsor provide written responses to all items above and FDA will provide further recommendations if needed.

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/s/

Maria Walsh
9/19/02 08:35:17 AM
CSO

Joyce Korvick
9/19/02 05:18:07 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: March 25, 2002

APPLICATION NUMBER: IND 46,656, Omeprazole Sodium Bicarbonate - Immediate Release, powder for suspension (OSB-IR (PWD

BETWEEN:

Name: Christine Simmons, Pharm D., Vice President, Regulatory Affairs & Quality Assurance
Phone: (858) 314-5731
Representing: Santarus, Inc.

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Feedback re: Proposed PK/PD study

BACKGROUND: Santarus, Inc. plans to conduct

The sponsor also plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study comparing OSB-IR (PWD to the listed drug product, Prilosec (omeprazole) Delayed-Release Capsules.

The sponsor submitted an outline of the planned PK/PD study to IND 46,656 (February 4, 2002; Serial No.16). The submission included the following two questions for Agency consideration:

1. Is it acceptable to the Agency that the test drugs in the proposed PK/PD trial be administered to fasted subjects, one hour before meals?
2. Does the Agency agree that there should be no requirement to study OSB-IR delivered concurrently with food?

TODAY'S CALL: I called Ms. Simmons and provided the following answers to the two questions above per e-mail communication, dated March 22, 2002, from Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer with concurrence from Dr. Suresh Doddapaneni, Team Leader, Biopharmaceutics.

1. It is acceptable that the proposed PK/PD study be conducted under fasting conditions.
2. The sponsor should evaluate the effect of food on the pharmacokinetics of OSB-IR.

IND 46,656

Page 2

I said if there were any further questions from the sponsor regarding the PK/PD study, they could be addressed at today's scheduled teleconference at 2:30 p.m. The call was then concluded.

/S/

Maria R. Walsh, M.S.
Regulatory Project Manager

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/s/

Maria Walsh
7/31/02 11:37:47 AM
CSO

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 20, 2003

Time: 10:00 AM

Location: Parklawn Building, 17th Floor, Conference Room 17-05

Application: IND 46,656

Type of Meeting: Type B; CMC

Meeting Chair: Liang Zhou, Ph.D.

Meeting Recorder: Melissa Furness, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Liang Zhou, Ph.D.	Chemistry Team Leader
Ray Frankewich	Chemistry Reviewer
Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Melissa Furness, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Santarus, Inc.

Warren Hall	VP, Product Development and Manufacturing
C. Simmons, PharmD	VP, Regulatory Affairs & QA
Debra Gessner	Director, Regulatory Affairs and QA
Laura Weston	Sr. Manager, Analytical Development & QC

Background:

The purpose of this meeting is to continue discussion and to provide CMC clarification regarding the sponsor's upcoming NDA submission.

Discussion Points:

Please find below our responses to the questions submitted in your February 17, 2003 Meeting Background Package. Our responses are in **bold**.

1. Submission Format

- Are there any preferences the Chemistry Reviewers would like to communicate with regard to content or format of an electronic submission using the ICH CTD format?

Copies in both Word 2000 and Acrobat would be ideal.

- Is a paper review copy of Module 3 requested?

Paper copy of Module 3 should not be necessary.

- May the Field Copy be submitted electronically?

Contact your local field office directly.

2. Section 3.2.P.3.3 Manufacturing Process and Process Controls [] Testing

Does the Agency agree that Santarus can adopt the [] testing plan in lieu of the []
[] Testing for Commercial Batches?

Consult directly with you local field office regarding your sampling for validation []

3. Section 3.2.P.2.3 Manufacturing Process Development and Section 3.2.P.3 Manufacture - []

Assuming supportive lot release data are provided in the NDA, does the Agency have any comments regarding the proposed []

[]

• []

• []

4. Does the Agency agree with the proposal that microbial limit testing not be conducted on commercial lots?

Submit complete data from the testing currently performed A decision will be reached after a review of the complete data.

5. Section 3.2.P.2.6 - Compatibility of Drug Product w/Constitution Diluent
Section 3.2.P.8.3 - Stability after Constitution/Photostability

Does the Agency agree that the data from the studies summarized above support the proposed directions for use?

Directions for use will be affected by many factors. The referenced data will be reviewed and considered.

Consider conducting a study that will demonstrate the range of pH values that will be neutralized by the sodium bicarbonate (consider EPA limits for pH for tap water). Consider temperature as a function of pH.

6. Section 3.2.P.5.1 - Drug Product Specifications

Does the Agency have any comments on the proposed NDA specifications?

The following comments are offered:

- We would suggest retaining the tests for Content Uniformity for sodium bicarbonate at release, stability batches, and dissolution. of sodium bicarbonate for
- Data for on stability batches should be submitted to the application, so that it may be evaluated.
- We recommend that you submit to the NDA data generated for release and stability for current batches of the drug product These data will be evaluated so that we may determine if specifications for these attributes are warranted.

Justification for the acceptance criterion for Total Impurities should be provided.

- The Agency find your proposed Sodium Bicarbonate Assay acceptable as long as you can provide us with data to scientifically justify it.

7. Section 3.2.P.2 Pharmaceutical Development – Palatability

Is the proposed support for the palatability of the suspension acceptable?

The palatability study appears reviewable.

**8. Section 3.2.P.2.3 Manufacturing Process Development and
Section 3.2.P.3 Manufacturer - Manufacturing Site, Process Scale and Equipment Changes**

Does the Agency agree with the proposal regarding submission of stability data supporting the manufacturing site change during the review of the NDA?

No. We recommend that you submit stability data as described in ICH Q1A (12 months Long-term, 6 months Accelerated) on at least three primary batches of drug product.

9. Section 3.2.P.7 Container Closure System

- Does the Agency agree that because the — product contact material is FDA-approved as a direct food grade material that no testing to quantify phenomena such as sorption and leaching have to be repeated by the sponsor?

A reference to the chapters of the CFR which pertain to substances that can be used as food-contact materials for the particular — that is proposed should be provided.

Testing to ensure that a proper dose is delivered from the package is advisable. If the drug product is to be reconstituted in its package, then studies to demonstrate that no leaching from the packaging components occurs should be provided.

- The sponsor proposes to demonstrate the effectiveness of the above-described container closure system by referencing data from ICH-compliant stability studies. Does the Agency have any comment on this proposal?

Please clarify.

- The sponsor proposes not to repeat because the product contact material is identical and the overall surface area equivalent to packet for which test data are available. Does the Agency agree with this proposal? J

Yes, this appears to be acceptable.

- For the purpose of demonstrating the equivalence of pre-commercial and commercial container closure submit — data from one lot of each dosage strength stored at accelerated stability conditions while the NDA is under review, as recommended by the FDA drug product stability expert panel at their March 31, 1999 meeting? J

No. See response to no. 8.

10. Section 3.2.P.8 Stability Program

Does the Agency agree with the proposal for submission of stability data for the proposed NDA?

No. See the response to question no. 8. Also, be advised that the accelerated stability condition recommended by ICH Q1A is 40°C/75%RH, not 40°C/30%RH as indicated above.

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MEMORANDUM OF MEETING MINUTES

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

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

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

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

Attendees:

Santarus, Inc.

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

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

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

Division of Pharmacological Evaluation II (HFD-870)

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

Division of Biometrics (HFD-715)

Thomas Permutt, Ph.D., Statistics Team Leader

Office of Generic Drugs (HFD-604)

Donald Hare

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

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

Santarus, Inc. submitted a meeting request and background package, dated August 31, 2001, for the purpose of discussing the clinical development plan for omeprazole sodium bicarbonate – immediate release, powder for suspension [OSB-IR (P.W.D.)]. The powder formulation will be suspended in water before administration. The sponsor plans to conduct a pharmacokinetic/pharmacodynamic (PK/PD) study comparing OSB-IR (P.W.D.) to the listed drug product, Prilosec (omeprazole) Delayed-Release Capsules. The sponsor also plans to

3 Protocol summaries of — studies were included in the background package.

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

Meeting objective: To discuss the clinical development plan for OSB-IR (P.W.D.).

Meeting summary:

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

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

Agenda items:

Biopharmaceutics (Protocol OSB-IR-CO2)

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

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

Agency Response:

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

Discussion:

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

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

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

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

Agency Response:

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

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

Agency Response:

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

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

Discussion:

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

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

Agency Response:

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

In addition, we request you conduct the following studies:

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

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Discussion:

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

to test the worst-case scenario.

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

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

Clinical/Statistics (Protocol OSB-IR [])

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Agency Response:

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Discussion:

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

8. Additional Agency Recommendations (CMC):

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

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

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

Discussion:

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

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

9. Additional Agency Recommendations (Pediatrics):

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

Discussion:

The sponsor said the proposed

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

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

10. Miscellaneous Issues:

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

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

Minutes Preparer:

Chair Concurrence:

Meeting Minutes

Page 9

Drafted: M.Walsh 12/6/01

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

S.Doddapaneni 12/7/01

T.Permutt 12/10/01

A.Shaw 12/10/01

L.Zhou 12/10/01

H.Gallo-Torres 12/10/01

D.Hare 12/6/01

J.Korvick 12/12/01

Final: M.Walsh 12/13/01

Filename: I46656.October1-2001.minutes.doc

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/s/

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