CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-849

CHEMISTRY REVIEW(S)

NDA 21-849

ZEGERID (OMEPRAZOLE) 20/40 mg Capsules

SANTARUS INC.

Maria E. Ysern, MSc.
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
BRANCH III

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-849

2. REVIEW #1

3. REVIEW DATE: November 30, 2005

4. REVIEWER: Maria E. Ysern.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Document	26-Apr-2005
BC Amendment	1-Nov-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Santarus, Inc
Address:	1590 West Ocean Air Drive, Suite 200 San Diego , California 92130
Representative:	Charles H. Davis, RAC Senior Director, Regulatory Affairs
Telephone:	(858) 314-5753

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Zegerid® Capsules
b) Non-Proprietary Name (USAN):	Omeprazole
c) Code Name/# (ONDC only):	OME-IR (CAP) or SAN-10
d) Chem. Type/Submission Priority (ONDC only):	Type 3, Standard.

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Inhibitor of gastric secretion

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 and 40 mg

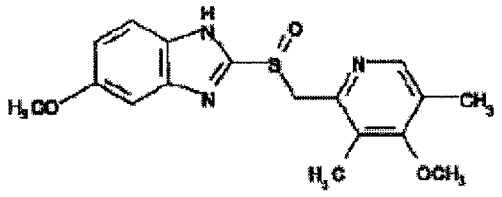
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_{17}H_{19}N_3O_3S$

17. RELATED/SUPPORTING DOCUMENTS:

4A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	[redacted]		3	Adequate	4/20/04	------
—				3	Adequate		

—		[redacted]	1	October 26,2005	Reviewed by Maria Ysern
—		[redacted]	3	Sep 15, 2000	Reviewed by the Bundle/Strike project
—		[redacted]	3	Sep 15, 2000	Reviewed by the Bundle/Strike project

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/A		
EES	Overall acceptable		
Pharm/Tox	pending		
Biopharm	pending		
LNC	N/A		
Methods Validation	pending		

DMETS	N/A		
EA	N/A		
Microbiology	N/A		

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Appears This Way
On Original

The Chemistry Review for NDA 21-849

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the information provided this NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUSTANCE:

Omeprazole, USP is the active ingredient in this immediate release formulation.
Chemical Name: R,S,-1-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl sulfinyl].
CAS number: [7390-58-6].
It is a white to off white powder with a melting range of 150-156 ° very slightly soluble in water. Omeprazole undergoes rapid degradation to cationic sulfonamide when exposed to acidic environments. It has a half life of less than 10 minutes at pH 4.
The production and manufacturing controls for the manufacturer of omeprazole drug substance are detailed in DMF# ——————————————.
All omeprazole specifications are based on current USP and ICH standards except for the specification for optical rotation and the ——— derived ————— specification. The omeprazole drug substance is ——————————.
A specification is in place to verify that a racemic omeprazole is used in the drug product rather than ——omeprazole. This test is performed by contract manufacturer and is not required for release by ———.
DMF —— was reviewed previously and found ADEQUATE.

DRUG PRODUCT :

Zegerid® Capsules is the proposed trade name and OME-IR (CAP) is the code name for the immediate release omeprazole capsule product. Zegerid® Capsules are manufactured in a size "—" hard gelatin capsules containing either 20 mg or 40 mg

omeprazole — , and 1100 mg of sodium bicarbonate (13.1 mEq), Croscaramellose Sodium —mg, and Magnesium stearate — .

The sodium bicarbonate in the Zegerid ® Capsule formulation protects the acid labile active ingredient from gastric acid degradation and distinguishes this omeprazole dosage form from delayed release capsules or tablets, which use enteric coatings to protect the omeprazole. Sodium Bicarbonate — was chosen for this drug product because of its —

Since no therapeutic claim is being made for the sodium bicarbonate component of this drug, this product currently — (This policy was discussed at a meeting October 1, 2003 for a now approved NDA 21-636 Omeprazole Sodium Bicarbonate IR Powder).

The drug product is packaged in a white, opaque — bottle — al for 30 count commercial packaging, and 30 mL for — count physician sample packaging) with a child resistant cap.
The Zegerid® Capsules are designed for quick dissolution in order to simultaneously release omeprazole and sodium bicarbonate into the stomach.
With the exception of Zegerid® Powder for Oral Suspension, all other omeprazole products currently marketed in the US are formulated as delayed release solid oral dosage forms containing enteric coated omeprazole (this protects but delays absorption.)
— omeprazole was used in the formulation in order to enhance the immediate release and rapid absorption characteristics. The — of the omeprazole — an important factor affecting bioavailability.
Given the importance of the sodium bicarbonate for its buffering capacity, acid neutralizing capacity of the Zegerid ® Capsules will be monitored at release

Expiration Dates for Zegerid®Capsules:

Dosage Strength	Packaging Configuration	Proposed Expiration Dating Period
20 mg	Physician Sample 5 Capsules/Bottle	— months
	Trade Product 30 Capsules/Bottle	— months
40 mg	Physician Sample 5 Capsules/Bottle	— months
	Trade Product 30 Capsules/Bottle	— months

B. Description of How the Drug Product is Intended to be Used

The Drug product is intended to be used orally. It is indicated for short term treatment (4-8 weeks) of active duodenal ulcer.

ZEGERID should be taken on an empty stomach at east one hour prior to meal and the capsule should be swallowed intact with water. Other liquids should not be used. The capsule should not be opened and contents sprinkled into food.

C. Basis for Approvability or Not-Approval Recommendation

Based on the information provided this NDA can be approved.

III. Administrative

A. Reviewer's Signature: In DFS

B. Endorsement Block

Chemist Name/Maria Ysern Date: October 26, 2005
ChemistryTeamLeader/Liang Zhou/Date October 26, 2005
Branch Chief/MooJhong Rhee/Date.
Project Manager/Mary Lewis/Date

C. CC Block see DFS

Chemistry Assessment

59 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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

/s/

Maria Ysern
11/30/2005 01:00:51 PM
CHEMIST
NDA 21-849

Liang Zhou
12/9/2005 03:05:44 PM
CHEMIST

#2

NDA 21-849

ZEGERID®Capsules (OMEPRAZOLE/Sodium bicarbonate) 20/40 mg

SANTARUS INC.

Maria E. Ysern, MSc.
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
BRANCH III

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-849

2. REVIEW # 2

3. REVIEW DATE: February 24, 2006

4. REVIEWER: Maria E. Ysern.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Document	26-Apr-2005
BC Amendment	1-Nov-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Santarus, Inc
Address:	1590 West Ocean Air Drive, Suite 200 San Diego , California 92130
Representative:	Charles H. Davis, RAC Senior Director, Regulatory Affairs
Telephone:	(858) 314-5753

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zegerid® Capsules
b) Non-Proprietary Name (USAN): Omeprazole/ Sodium bicarbonate
c) Code Name/# (ONDC only): OME-IR (CAP) or SAN-10
d) Chem. Type/Submission Priority (ONDC only): Changed from Type 3 toType 4 (As of February 23), Standard.

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Inhibitor of gastric secretion

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 and 40 mg of omeprazole
1100 mg of sodium bicarbonate per capsule

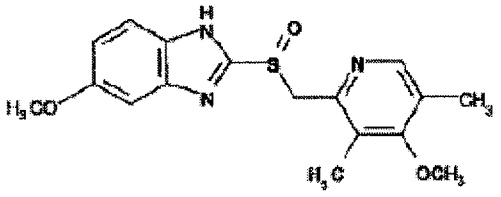
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_{17}H_{19}N_3O_3S$

17. RELATED/SUPPORTING DOCUMENTS:
4A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	⌐	⌐	3	Adequate	4/20/04	------

—			3	Adequate		
—				1	October 26,2005	Reviewed by Maria Ysern
—				3	Sep 15, 2000	Reviewed by the Bundle/Strike project
—				3	Sep 15, 2000	Reviewed by the Bundle/Strike project

[1] Action codes for DMF Table:
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/A		
EES	Overall acceptable	Feb 24, 2006	
Pharm/Tox			

Biopharm			
LNC	N/A		
Methods Validation	pending		
DMETS	N/A		
EA	N/A		
Microbiology	N/A		

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-849

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Based on the information provided this NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
No recommendations from the CMC standpoint.

II. Summary of Chemistry Assessments

Comment:
As of February 2005 it was decided that Zegerid is a combination product containing two active ingredients, omeprazole and sodium bicarbonate.
An inspection for ——— manufacturers of sodium bicarbonate, was submitted and found acceptable. (Refer to attached e-mail dated Feb 23, 2006 from Concepcion Cruz).

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUSTANCES:
•Omeprazole, USP is one of the active ingredient in this immediate release formulation.
Chemical Name: R,S,-1-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl sulfinyl].
CAS number: [7390-58-6].
It is a white to off white powder with a melting range of 150-156 ° very slightly soluble in water. Omeprazole undergoes rapid degradation to cationic sulfonamide when exposed to acidic environments. It has a half life of less than 10 minutes at pH 4.
The production and manufacturing controls for the manufacturer of omeprazole drug substance are detailed in DMF# ———.
All omeprazole specifications are based on current USP and ICH standards except for the specification for optical rotation and the ——— derived ———— specification. The omeprazole drug substance is ———.
A specification is in place to verify that a racemic omeprazole is used in the drug product rather than ——omeprazole. This test is performed by contract manufacturer and is not required for release by ———

DMF —— was reviewed previously and found ADEQUATE.

•Sodium Bicarbonate (Na_2CO_3) is the other active ingredient. CAS-144-55-8.
Each capsule contains 1100 mg of sodium bicarbonate.

DRUG PRODUCT :

Zegerid® Capsules is the proposed trade name and OME-IR (CAP) is the code name for the immediate release omeprazole capsule product. Zegerid® Capsules are manufactured in a size —" hard gelatin capsules containing either 20 mg or 40 mg omeprazole —, and 1100 mg of sodium bicarbonate — (13.1 mEq), Croscaramellose Sodium — ng, and Magnesium stearate —— .

The other active substance, sodium bicarbonate,in the Zegerid ® Capsule formulation protects the acid labile active ingredient from gastric acid degradation and distinguishes this omeprazole dosage form from delayed release capsules or tablets, which use enteric coatings to protect the omeprazole. Sodium Bicarbonate —— as chosen for this drug product because of its ——

The drug product is packaged in a white, opaque ——
bottle — l for 30 count commercial packaging, and — L for 5 count physician sample packaging) with a child resistant cap.
The Zegerid® Capsules are designed for quick dissolution in order to simultaneously release omeprazole and sodium bicarbonate into the stomach.
With the exception of Zegerid® Powder for Oral Suspension, all other omeprazole products currently marketed in the US are formulated as delayed release solid oral dosage forms containing enteric coated omeprazole (this protects but delays absorption.)
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ZEGERID should be taken on an empty stomach at east one hour prior to meal and the capsule should be swallowed intact with water. Other liquids should not be used.
The capsule should not be opened and contents sprinkled into food.

C. Basis for Approvability or Not-Approval Recommendation
Based on the information provided, this NDA can be approved.

III. Administrative

A. Reviewer's Signature: In DFS

B. Endorsement Block (review #2)

Chemist Name/Maria Ysern Date:Feb 24, 2005
Chemistry Team Leader/Liang Zhou/Date Feb 24, 2005
Branch Chief/MooJhong Rhee/Date.
Project Manager/Mary Lewis/Date

C. CC Block see DFS

Chemistry Assessment

63 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Maria Ysern
2/24/2006 09:12:38 AM
CHEMIST

Moo-Jhong Rhee
2/24/2006 10:04:46 AM
CHEMIST
Chief, Branch III

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