

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-456

CHEMISTRY REVIEW(S)



CMC REVIEW



NDA 22-456

OMEPRAZOLE/SODIUM BICARBONATE/ MAGNESIUM HYDROXIDE

Tablets

20mg/750mg/343mg

40mg/750mg/343mg

SANTARUS Inc.

Tarun Mehta

Review Chemist

**Branch III/Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 22-456
For the Division of Gastroenterology Products (HFD-180)**

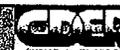


Table of Contents

Table of Contents2

CMC Review Data Sheet4

The Executive Summary8

I. Recommendations8

 A. Recommendation and Conclusion on Approvability 8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

II. Summary of CMC Assessments.....8

 A. Description of the Drug Product(s) and Drug Substance(s)..... 8

 B. Description of How the Drug Product is Intended to be Used..... 9

 C. Basis for Approvability or Not-Approval Recommendation..... 9

III. Administrative.....10

CMC Assessment..... 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....11

S DRUG SUBSTANCE (Omeprazole)..... 11

 S.1 General Information11

 S.2 Manufacture11

 S.3 Characterization11

 S.4 Control of Drug Substance.....11

 S.5 Reference Standards or Materials11

 S.6 Container Closure System.....11

 S.7 Stability11

S DRUG SUBSTANCE (Sodium Bicarbonate USP)..... 11

S DRUG SUBSTANCE (Magnesium Hydroxide)..... 11

P DRUG PRODUCT : Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets..... 12

 P.1 Description and Composition of the Drug Product12

 P.2 Pharmaceutical Development.....12

 P.3 Manufacture12

 P.4 Control of Excipients12

 P.5 Control of Drug Product12

 P.6 Reference Standards or Materials12

 P.7 Container Closure System.....12

 P.8 Stability12

A APPENDICES 12

b(4)



R REGIONAL INFORMATION 12

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 113

 A. Labeling & Package Insert..... 13

 B. Environmental Assessment Or Claim Of Categorical Exclusion 17

III. List Of Deficiencies to be Communicated: None18

IV. Attachment18



CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-456
2. REVIEW #: 3
3. REVIEW DATE: 03-Dec-2009
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	January 28, 2009
Amendment0007 (BZ)	June 03, 2009
Amendment0011 (QT)	August 26, 2009
Amendment0014 (BC)	October 13, 2009
Amendment0015 (BC)	October 28, 2009
Amendment 0020	November 30, 2009
Amendment 0021	December 03, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus Inc.
Address: 3721 Valley Center Drive, Suite 400 San Diego,
CA 92130
Representative: Maria Boyda-Toro, Ph.D., M.B.A.
Telephone: (858) 314-5715

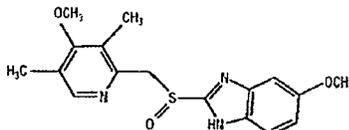
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets
- b) Non-Proprietary Name: Omeprazole/sodium bicarbonate/magnesium hydroxide
- c) Code Name/# (ONDQA only): SAN-20
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: Standard

CMC Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Proton pump inhibitor
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20mg/750mg/343mg, 40mg/750mg/343mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

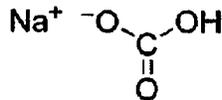
STRUCTURE (OMEPRAZOLE \longrightarrow), **b(4)**



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

Molecular Weight: 345.42

STRUCTURE (SODIUM BICARBONATE \longrightarrow), **b(4)**



Molecular Formula: $NaHCO_3$

Molecular Weight: 84.01

STRUCTURE (MAGNESIUM HYDROXIDE \longrightarrow), **b(4)**



CMC Review Data Sheet

The magnesium hydroxide drug substance used in the Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets is magnesium hydroxide _____
 The structure listed below refers to the active portion of the drug substance, magnesium hydroxide.
 Structure: HO-Mg-OH
 Molecular Formula: Mg(OH)₂
 Molecular Weight: 58.32

b(4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	Aug-08-2007 by Sema Basaran	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Sept-24-2001	No update since last review
					Adequate	Mar-12-2009 By Bogdan Kurtylca	No update since last review
					Adequate	Sept-09-2007 by Bartha Craig	No update since last review
					Adequate		
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Feb-05-2007 by Arthur Shaw	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate		
					Adequate	Jan-04-2004 by Monica Cooper	No update since last review

b(4)

b(4)

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF



CMC Review Data Sheet

- 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:

Application Identification	Document Type
IND 46,656	Investigational New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
IND 65,687	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets
IND 69,937	Investigational New Drug Application for ZEGERID® Capsules
IND 75,432	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Tablets
NDA 19-810	Prilosec Delayed Release Capsules
NDA 21-636	New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
NDA 21-849	New Drug Application for ZEGERID® Capsules
NDA 21-850	New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12/02/09	A. Inyard (HFD-320)
EA	Categorical exclusion is granted (see p. 71)	10/29/09	Tarun Mehta



Executive Summary Section

The CMC Review for NDA 22-456

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An overall "Acceptable" recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

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

Not applicable

II. Summary of CMC Assessments

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

(1) Drug Substances

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets formulation contains three drug substances: omeprazole USP, sodium bicarbonate USP, and magnesium hydroxide [redacted] Omeprazole a proton pump inhibitor is considered as a primary drug substance. The function of the other two drug substances is to protect the acid labile omeprazole by neutralizing the gastric pH level. The drug substance magnesium hydroxide [redacted] is non compendial material, however its [redacted] magnesium hydroxide is compendial (USP) grade. Adequate chemistry, manufacturing and controls information for all three drug substances is provided either in the DMF or through the NDA. All three drug substances are freely soluble in water. The quality of the drug substances is controlled by the compendial (USP) monographs. Based on the stability data, adequate re-test period are established by the manufacturers: [redacted] for omeprazole USP and sodium bicarbonate USP, and [redacted] for magnesium hydroxide [redacted]

b(4)

b(4)

b(4)

(2) Drug Product



Executive Summary Section

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets contains omeprazole 20mg or 40mg, sodium bicarbonate 750mg and magnesium hydroxide 343mg (equivalent to _____ of magnesium hydroxide _____)

b(4)

The drug product is an immediate-release, white oval shaped tablet embossed with "ZM 20" for the 20 mg strength and "ZM 40" for the 40 mg strength on one side of the tablet. The drug product is supplied in a _____ bottle of 30 tablets for commercial use or _____ bottle of _____. The container/closure system is a HDPE bottle _____.

b(4)

The composition and manufacturing process of the clinical batches and proposed commercial batches are identical. All the excipients used in the drug product are compendial (USP/NF) grade. All the excipients are listed in the FDA inactive ingredient list and have been used in the previously drug products at or below the proposed concentration. The drug product is manufactured by _____.

b(4)

The drug product was developed to achieve rapid dissolution and absorption (*in-vivo*) of omeprazole in gastric environment. To achieve this the sponsor has used _____ omeprazole. The identity, strength, purity and quality of the final drug product are assured by the specification: appearance, ID, content uniformity, weight variation, assay of APIs and related substances, dissolution, _____ and acid neutralization capacity. Based on available stability data, the expiration dating period of 18 months is granted for 40mg tablets and nine (9) months for 20mg tablets.

b(4)

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

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets is indicated for short-term treatment of active duodenal ulcer, (4 - 8 weeks, 20mg tablet once daily), short-term treatment of active benign gastric ulcer (40mg tablet once daily, 4-8 weeks), for the treatment of Gastroesophageal Reflux Disease (GERD) and other symptoms associated with GERD (20mg tablet once daily for 4-8 weeks). Also indicated for the short-term treatment of erosive esophagitis (20mg tablet once daily for 4-8 weeks) and maintenance of Healing of Erosive Esophagitis (20mg tablet once daily).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All the facilities have acceptable site recommendations.
All labels have required information.



Executive Summary Section

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III/DPA II, ONDQA

C. CC Block: entered electronically in DFS

8 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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

/s/

TARUN D MEHTA
12/03/2009

MOO JHONG RHEE
12/03/2009
Chief, Branch III



CMC REVIEW



NDA 22-456

OMEPRAZOLE/SODIUM BICARBONATE/ MAGNESIUM HYDROXIDE

Tablets

20mg/750mg/343mg

40mg/750mg/343mg

SANTARUS Inc.

Tarun Mehta

Review Chemist

**Branch III/Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 22-456
For the Division of Gastroenterology Products (HFD-180)**

Table of Contents

Table of Contents2

CMC Review Data Sheet.....4

The Executive Summary8

I. Recommendations8

 A. Recommendation and Conclusion on Approvability 8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

II. Summary of CMC Assessments.....8

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 B. Description of How the Drug Product is Intended to be Used..... 9

 C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative.....10

CMC Assessment..... 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....11

S DRUG SUBSTANCE (Omeprazole)..... 11

 S.1 General Information 11

 S.2 Manufacture 11

 S.3 Characterization 11

 S.4 Control of Drug Substance..... 11

 S.5 Reference Standards or Materials 11

 S.6 Container Closure System 11

 S.7 Stability 11

S DRUG SUBSTANCE (Sodium Bicarbonate USP) 11

S DRUG SUBSTANCE (Magnesium Hydroxide) 11

P DRUG PRODUCT : Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets 12

 P.1 Description and Composition of the Drug Product 12

 P.2 Pharmaceutical Development 12

 P.3 Manufacture 12

 P.4 Control of Excipients 12

 P.5 Control of Drug Product 12

 P.6 Reference Standards or Materials 12

 P.7 Container Closure System 12

 P.8 Stability 12

A APPENDICES 12

b(4)



R REGIONAL INFORMATION..... 12

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 113

 A. Labeling & Package Insert..... 13

 B. Environmental Assessment Or Claim Of Categorical Exclusion 17

III. List Of Deficiencies to be Communicated: None17

IV. Attachment17



CMC Review Data Sheet

1. NDA 22-456
2. REVIEW #: 2
3. REVIEW DATE: 01-Dec-2009
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	January 28, 2009
Amendment0007 (BZ)	June 03, 2009
Amendment0011 (QT)	August 26, 2009
Amendment0014 (BC)	October 13, 2009
Amendment0015 (BC)	October 28, 2009
Amendment 0019	November 30, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus Inc.
 Address: 3721 Valley Center Drive, Suite 400 San Diego,
 CA 92130
 Representative: Maria Boyda-Toro, Ph.D., M.B.A.
 Telephone: (858) 314-5715

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets
- b) Non-Proprietary Name: Omeprazole/sodium bicarbonate/magnesium hydroxide
- c) Code Name/# (ONDQA only): SAN-20
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

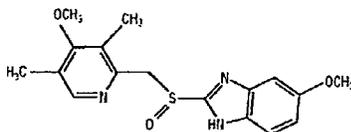
CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Proton pump inhibitor
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20mg/750mg/343mg, 40mg/750mg/343mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

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

STRUCTURE (OMEPRAZOLE) 

b(4)

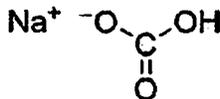


Molecular Formula: C₁₇H₁₉N₃O₃S

Molecular Weight: 345.42

STRUCTURE (SODIUM BICARBONATE) 

b(4)



Molecular Formula: NaHCO₃

Molecular Weight: 84.01

STRUCTURE (MAGNESIUM HYDROXIDE) 

b(4)



CMC Review Data Sheet

The magnesium hydroxide drug substance used in the Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets is magnesium hydroxide:

The structure listed below refers to the active portion of the drug substance, magnesium hydroxide.

Structure: HO-Mg-OH

Molecular Formula: Mg(OH)₂

Molecular Weight: 58.32

b(4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	Aug-08-2007 by Sema Basaran	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Sept-24-2001	No update since last review
					Adequate	Mar-12-2009 By Bogdan Kurtylca	No update since last review
					Adequate	Sept-09-2007 by Bartha Craig	No update since last review
					Adequate		
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Feb-05-2007 by Arthur Shaw	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate		
					Adequate	Jan-04-2004 by Monica Cooper	No update since last review

b(4)

b(4)

b(4)

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



CMC Review Data Sheet

- 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:

Application Identification	Document Type
IND 46,656	Investigational New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
IND 65,687	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets
IND 69,937	Investigational New Drug Application for ZEGERID® Capsules
IND 75,432	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Tablets
NDA 19-810	Prilosec Delayed Release Capsules
NDA 21-636	New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
NDA 21-849	New Drug Application for ZEGERID® Capsules
NDA 21-850	New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	WITHHOLD	11/25/09	E.Johnson (HFD-320)
EA	Categorical exclusion is granted (see p. 71)	10/29/09	Tarun Mehta



Executive Summary Section

The CMC Review for NDA 22-456

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. However, an overall "WITHHOLD" recommendation from the Office of Compliance has been made due to the drug substance manufacturer.

Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

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

Not applicable

II. Summary of CMC Assessments

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

(1) Drug Substances

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets formulation contains three drug substances: omeprazole USP, sodium bicarbonate USP, and magnesium hydroxide _____ Omeprazole a proton pump inhibitor is considered as a primary drug substance. The function of the other two drug substances is to protect the acid labile omeprazole by neutralizing the gastric pH level. The drug substance magnesium hydroxide _____ is non compendial material, however its starting material magnesium hydroxide is compendial (USP) grade. Adequate chemistry, manufacturing and controls information for all three drug substances is provided either in the DMF or through the NDA. All three drug substances are freely soluble in water. The quality of the drug substances is controlled by the compendial (USP) monographs. Based on the stability data, adequate re-test period are established by the manufacturers: _____ for omeprazole USP and sodium bicarbonate USP, and _____ for magnesium hydroxide _____

b(4)

b(4)

b(4)



Executive Summary Section

(2) Drug Product

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets contains omeprazole 20mg or 40mg, sodium bicarbonate 750mg and magnesium hydroxide 343mg (equivalent to _____ of magnesium hydroxide _____). The drug product is an immediate-release, white oval shaped tablet embossed with "ZM 20" for the 20 mg strength and "ZM 40" for the 40 mg strength on one side of the tablet. The drug product is supplied in a _____ bottle of 30 tablets for commercial use or _____. The container/closure system is a HDPE bottle _____. The composition and manufacturing process of the clinical batches and proposed commercial batches are identical. All the excipients used in the drug product are compendial (USP/NF) grade. All the excipients are listed in the FDA inactive ingredient list and have been used in the previously drug products at or below the proposed concentration. The drug product is manufactured by _____. The drug product was developed to achieve rapid dissolution and absorption (*in-vivo*) of omeprazole in gastric environment. To achieve this the sponsor has used _____ omeprazole. The identity, strength, purity and quality of the final drug product are assured by the specification: appearance, ID, content uniformity, weight variation, assay of APIs and related substances, dissolution, _____ and acid neutralization capacity. Based on available stability data, the expiration dating period of 18 months is granted for 40mg tablets and nine (9) months for 20mg tablets.

b(4)

b(4)

b(4)

b(4)

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

Omeprazole/Sodium bicarbonate/Magnesium hydroxide Tablets is indicated for short-term treatment of active duodenal ulcer, (4 - 8 weeks, 20mg tablet once daily), short-term treatment of active benign gastric ulcer (40mg tablet once daily, 4-8 weeks), for the treatment of Gastroesophageal Reflux Disease (GERD) and other symptoms associated with GERD (20mg tablet once daily for 4-8 weeks). Also indicated for the short-term treatment of erosive esophagitis (20mg tablet once daily for 4-8 weeks) and maintenance of Healing of Erosive Esophagitis (20mg tablet once daily).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All labels have required information.



Executive Summary Section

However, an overall "WITHHOLD" recommendation from the Office of Compliance has been made for the drug substance [Magnesium Hydroxide _____] _____ manufacturer.

b(4)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III/DPA II, ONDQA

C. CC Block: entered electronically in DFS

7 Page(s) Withheld

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

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22456

ORIG-1

SANTARUS INC

ZEGERID

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

/s/

TARUN D MEHTA

12/01/2009

MOO JHONG RHEE

12/01/2009

Chief, Branch III



CMC REVIEW



NDA 22-456

Trademark

(omeprazole, sodium bicarbonate, magnesium hydroxide) Tablets

20mg/750mg/343mg

40mg/750mg/343mg

SANTARUS Inc.

Tarun Mehta

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III**

**CMC REVIEW OF NDA 22-456
For the Division of Gastroenterology Products (HFD-180)**

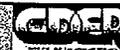


Table of Contents

Table of Contents2

CMC Review Data Sheet4

The Executive Summary8

I. Recommendations8

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 C. Basis for Approvability or Not-Approval Recommendation..... 9

III. Administrative.....10

CMC Assessment..... 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data11

S DRUG SUBSTANCE..... 11

 S.1 General Information11

 S.2 Manufacture11

 S.3 Characterization12

 S.4 Control of Drug Substance13

 S.5 Reference Standards or Materials14

 S.6 Container Closure System14

 S.7 Stability15

P DRUG PRODUCT 15

 P.1 Description and Composition of the Drug Product25

 P.2 Pharmaceutical Development.....26

 P.3 Manufacture32

 P.4 Control of Excipients34

 P.5 Control of Drug Product35

 P.6 Reference Standards or Materials51

 P.7 Container Closure System51

 P.8 Stability57

A APPENDICES 65

 A.1 Facilities and Equipment (biotech only)65

 A.2 Adventitious Agents Safety Evaluation65

 A.3 Novel Excipients65

R REGIONAL INFORMATION 65

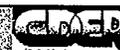


R1 Executed Batch Records65
R2 Comparability Protocols66
R3 Methods Validation Package66

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 167

 A. Labeling & Package Insert..... 67
 B. Environmental Assessment Or Claim Of Categorical Exclusion 71

III. List Of Deficiencies to be Communicated.....71



CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-456
2. REVIEW #: 1
3. REVIEW DATE: 29-Oct-2009
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	January 28, 2009
Amendment0007 (BZ)	June 03, 2009
Amendment0011 (QT)	August 26, 2009
Amendment0014 (BC)	October 13, 2009
Amendment0015 (BC)	October 28, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus Inc.
Address: 3721 Valley Center Drive, Suite 400 San Diego,
CA 92130
Representative: Maria Boyda-Toro, Ph.D., M.B.A.
Telephone: (858) 314-5715

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Trademark
- b) Non-Proprietary Name: Omeprazole/sodium bicarbonate/magnesium hydroxide
- c) Code Name/# (ONDQA only): SAN-20
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: Standard

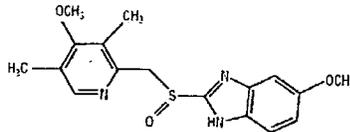
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)



CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Proton pump inhibitor
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 20mg/750mg/343mg, 40mg/750mg/343mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

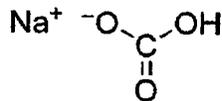
STRUCTURE (OMEPRAZOLE, ~~_____~~) **b(4)**



Molecular Formula: C₁₇H₁₉N₃O₃S

Molecular Weight: 345.42

STRUCTURE (SODIUM BICARBONATE, ~~_____~~) **b(4)**



Molecular Formula: NaHCO₃

Molecular Weight: 84.01

STRUCTURE (MAGNESIUM HYDROXIDE, ~~_____~~) **b(4)**



CMC Review Data Sheet

The magnesium hydroxide drug substance used in the Trademark® Tablets is magnesium hydroxide _____ The structure listed below refers to the active portion of the drug substance, magnesium hydroxide.

b(4)

Structure: HO-Mg-OH

Molecular Formula: Mg(OH)₂

Molecular Weight: 58.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	Aug-08-2007 by Sema Basaran	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Octo-19-2009 by Tarun Mehta	No update since last review
					Adequate	Sept-24-2001	No update since last review
					Adequate	Mar-12-2009 By Bogdan Kurtylca	No update since last review
					Adequate	Sept-09-2007 by Bartha Craig	No update since last review
					Adequate		
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Feb-05-2007 by Arthur Shaw	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate	Dec-7-2004 by Rapti Madurawe	No update since last review
					Adequate		
					Adequate	Jan-04-2004 by Monica Cooper	No update since last review

b(4)

b(4)

b(4)

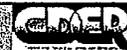
¹ Action codes for DMF Table:

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



CMC Review Data Sheet

- 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:

Application Identification	Document Type
IND 46,656	Investigational New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
IND 65,687	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets
IND 69,937	Investigational New Drug Application for ZEGERID® Capsules
IND 75,432	Investigational New Drug Application for ZEGERID® with Magnesium Hydroxide Tablets
NDA 19-810	Prilosec Delayed Release Capsules
NDA 21-636	New Drug Application for ZEGERID® Powder for Oral Suspension (POS)
NDA 21-849	New Drug Application for ZEGERID® Capsules
NDA 21-850	New Drug Application for ZEGERID® with Magnesium Hydroxide Chewable Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	10/29/09	
EA	Categorical exclusion is granted (see p. 71)	10/29/09	Tarun Mehta



Executive Summary Section

The CMC Review for NDA 22-456

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. However, an overall "Acceptable" recommendation from the Office of Compliance has not been made as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability is established.

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

Not applicable

II. Summary of CMC Assessments

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

(1) Drug Substances

Trademark tablet formulation contains three drug substances: omeprazole USP, sodium bicarbonate USP, and magnesium hydroxide _____
Omeprazole a proton pump inhibitor is considered as a primary drug substance. The function of the other two drug substances is to protect the acid labile omeprazole by neutralizing the gastric pH level. The drug substance magnesium hydroxide _____
_____ is non compendial material, however its _____
magnesium hydroxide is compendial (USP) grade. Adequate chemistry, manufacturing and controls information for all three drug substances is provided either in the DMF or through the NDA. All three drug substances are freely soluble in water. The quality of the drug substances is controlled by the compendial (USP) monographs. Based on the stability data, adequate re-test period are established by the manufacturers: _____ for omeprazole USP and sodium bicarbonate USP, and _____ for magnesium hydroxide s: _____

b(4)

b(4)

b(4)

(2) Drug Product



Executive Summary Section

Trademark tablet contains omeprazole 20mg or 40mg, sodium bicarbonate 750mg and magnesium hydroxide 343mg (equivalent to _____ of magnesium hydroxide _____). The drug product is an immediate-release, white oval shaped tablet embossed with "ZM 20" for the 20 mg strength and "ZM 40" for the 40 mg strength on one side of the tablet. The drug product is supplied in a _____ bottle of 30 tablets for commercial use or _____

b(4)

_____ The container/closure system is a HDPE bottle _____

b(4)

_____ The composition and manufacturing process of the clinical batches and proposed commercial batches are identical. All the excipients used in the drug product are compendial (USP/NF) grade. All the excipients are listed in the FDA inactive ingredient list and have been used in the previously drug products at or below the proposed concentration. The drug product is manufactured by _____ The drug product was developed to achieve rapid dissolution and absorption (*in-vivo*) of omeprazole in gastric environment. To achieve this the sponsor has used _____

b(4)

_____ omeprazole. The identity, strength, purity and quality of the final drug product are assured by the specification: appearance, ID, content uniformity, weight variation, assay of APIs and related substances, dissolution, _____ and acid neutralization capacity. Based on available stability data, the expiration dating period of 18 months is granted for 40mg tablets and nine (9) months for 20mg tablets.

b(4)

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

_____ is indicated for short-term treatment of active duodenal ulcer, (4 - 8 weeks, 20mg tablet once daily), short-term treatment of active benign gastric ulcer (40mg tablet once daily, 4-8 weeks), for the treatment of Gastroesophageal Reflux Disease (GERD) and other symptoms associated with GERD (20mg tablet once daily for 4-8 weeks). Also indicated for the short-term treatment of erosive esophagitis (20mg tablet once daily for 4-8 weeks) and maintenance of Healing of Erosive Esophagitis (20mg tablet once daily).

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All labels have required information.

However, an overall "Acceptable" recommendation from the office of compliance is still pending.



Executive Summary Section

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III/DPA II, ONDQA

C. CC Block: entered electronically in DFS

61 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22456	ORIG-1	SANTARUS INC	ZEGERID

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

/s/

TARUN D MEHTA
11/18/2009

MOO JHONG RHEE
11/18/2009
Chief, Branch III