

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-636**

**Chemistry Review(s)**

## ADDENDUM

**FROM:** Marie Kowblansky, Chemistry Reviewer

**THROUGH:** Liang Zhou, Chemistry Team Leader, HFD-180

**TO:** NDA 21-636

In the final CMC review of this NDA, dated April 22, 2004, it was concluded that all CMC issues were resolved and that the NDA could be approved from a CMC perspective. The only issues that needed to be resolved were labeling issues, as described below:

1. The applicant was requested to list all product components on the immediate package label. The applicant has agreed to do so, and this is considered acceptable.
2. The applicant wishes to include the immediate release designation in the product name, i.e. "TRADE NAME Immediate Release Powder for Oral Suspension". Although the delayed release designation is included in product names, it is not our practice to include the immediate release designation. For this reason DMETS has recommended removal of "immediate release" from the product name. Yana Mille, Chief of CDER Compendial Operations, was of the same opinion, i.e. that "immediate release" should not be part of the established name. Consequently, the CMC recommendation is that "immediate release" should be removed from the product established name.

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/s/

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Marie Kowblansky  
5/28/04 01:21:01 PM  
CHEMIST

Liang Zhou  
5/28/04 02:02:39 PM  
CHEMIST

**THERE ARE ONLY TWO CHEMISTRY REVIEWS – CMC  
NUMBER #3 IS A TYPO AND SHOULD BE CMC #2**

**NDA 21-636**

**Omeprazole  
Immediate-Release Powder for Oral Suspension  
(20 mg single dose packets)**

**Santarus, Inc.**

**Marie Kowblansky, Ph.D.  
DIVISION OF GASTROINTESTINAL AND COAGULATION  
DRUG PRODUCTS**

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# Chemistry Review Data Sheet

1. NDA 21-636

2. REVIEW #: 3

3. REVIEW DATE: April 20, 2004

4. REVIEWER: Marie Kowblansky, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

August 15, 2003

BC

February 23, 2004

BC

April 7, 2004

BC

April 19, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus, Inc.

Address: 10590 West Ocean Air Drive, Suite 200  
San Diego, California

Representative: Bonnie Hepburn, MD

Telephone: 858-314-5731

Fax: 858-314-5701

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be determined
- b) Non-Proprietary Name (USAN): omeprazole
- c) Code Name/# (ONDCS only): NA
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This is a 505(b)(2) application where the reference approved drug product is Astra Zeneca's Prilosec.

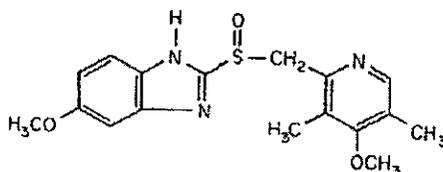
# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

10. **PHARMACOL. CATEGORY:** treatment of duodenal ulcer, gastroesophageal reflux disorder (GERD), erosive esophagitis
11. **DOSAGE FORM:** immediate release powder for oral suspension
12. **STRENGTH/POTENCY:** 20 mg per packet
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:**

**CHEMICAL NAME:** 5-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-benzimidazole



**MOLECULAR FORMULA:** C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S

**MOLECULAR WEIGHT:** 345.42

17. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	1	/	Drug substance	1	Adequate	4/20/04	-----
2	3	/		4			

<sup>1</sup> 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")

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

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

### B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-706	<ul style="list-style-type: none"><li>40 mg omeprazole immediate release powder for oral suspension.</li><li>Application was submitted 2/27/04 and has not yet been reviewed</li></ul>
IND	46,656	omeprazole immediate release powder for oral suspension

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	11/14/03	S. Ferguson
Pharm/Tox	Not Applicable		
Biopharm	Pending		S. Al-Fayoumi
LNC	Not Applicable		
Methods Validation	Not required		
DMETS	pending		
EA	Not required*	3/5/04	M. Kowblansky
Microbiology	Not Applicable		

\*The applicant appropriately claims categorical exclusion on the basis that the concentration of the active moiety will not exceed 1 ppb at the point of entry into the aquatic environment

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# The Chemistry Review for NDA 21-372

## The Executive Summary

### I. Recommendations

- A. From the chemistry perspective, this application may be Approved. However, labeling negotiations are still in progress with the applicant.

A recommendation that the applicant petition USP to update the USP monograph for omeprazole should be included in the approval letter.

- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable** – No post-approval commitments are required at the present time.

### II. Summary of Chemistry Assessments

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

The drug product is provided in single-use, child-resistant packets containing 20 mg of omeprazole USP, 1680 mg of sodium bicarbonate USP, flavors, and other excipients. The packaging is designed to protect the product from moisture and light. Prior to administration, the contents of one packet are constituted with water [ ]

According to the applicant, the function of the sodium bicarbonate in this immediate release formulation is to protect the active ingredient from gastric degradation, by increasing the pH of the stomach. This distinguishes this proposed immediate release dosage form from the delayed release solid oral dosage forms of omeprazole currently on the market, which are enteric coated to prevent dissolution of the tablet in the stomach.

To ensure that the full 20 mg dose is administered to the patient, the applicant proposes to manufacture the product with a [ ] of omeprazole in the formulation [ ]

with [ ] of the formulated powder [ ] Initially, the applicant proposed [ ]

[ ] However, data submitted in the application do not support use of [ ] for the three commercial-scale batches manufactured by the applicant, the data show that [ ] omeprazole were recovered from the packets. Consequently, the applicant has agreed to our recommendation that [ ] be eliminated from the manufacturing process.

The applicant has appropriately requested an 18-month expiration period for the drug product, with controlled room temperature storage. The [ ] stability data at controlled room temperature and [ ] accelerated stability data (40 degrees Centigrade) submitted with the application support this request. The data show no trends indicative of unusual instability, and suggest that with the submission of longer term stability data, expiration may be extended.

The active drug substance is omeprazole, a racemic mixture of two enantiomers, which is also the active ingredient in a number of new and generic products currently on the market. Omeprazole is unstable under acidic conditions, but its stability increases with increasing pH. To provide fast dissolution in the stomach and enhanced bio-absorption, [ ]

Chemistry Assessment Section

omeprazole is used in the formulation.

*NOTE: The applicant makes repeated references to a higher dose formulation containing 40 mg of omeprazole per packet. Since this NDA is for a single product that contains 20 mg of omeprazole per packet, the information regarding the higher dose formulation has not been carefully reviewed, but has been used as supporting information, where appropriate.*

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

The dosing instructions call for constituting the entire contents of the packet in 1-2 tablespoons of water, [ ] and drinking immediately. The instructions further direct to refill the container with water and drink. The label contains a cautionary statement not to substitute other liquids or foods for the water.

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

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemistry Reviewer: Marie Kowblansky, Ph.D.

ChemistryTeamLeader: Liang Zhou, Ph.D.

ProjectManager: Susan Daugherty

**C. CC Block**

4 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

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Marie Kowblansky  
4/22/04 04:32:05 PM  
CHEMIST

Liang Zhou  
4/22/04 05:17:49 PM  
CHEMIST

**NDA 21-636**

**Omeprazole  
Immediate-Release Powder for Oral Suspension  
(20 mg single dose packets)**

**Santarus, Inc.**

**Marie Kowblansky, Ph.D.  
DIVISION OF GASTROINTESTINAL AND COAGULATION  
DRUG PRODUCTS**



**CHEMISTRY REVIEW**

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Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 21-636
2. REVIEW #: 1
3. REVIEW DATE: March 5, 2004, 2004
4. REVIEWER: Marie Kowblansky, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original  
BC

Document Date

August 15, 2003  
February 23, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus, Inc.

Address: 10590 West Ocean Air Drive, Suite 200  
San Diego, California

Representative: Bonnie Hepburn, MD

Telephone: 858-314-5731

Fax: 858-314-5701

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be determined
- b) Non-Proprietary Name (USAN): omeprazole
- c) Code Name/# (ONDCS only): NA
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This is a 505(b)(2) application where the reference approved drug product is Astra Zeneca's Prilosec.

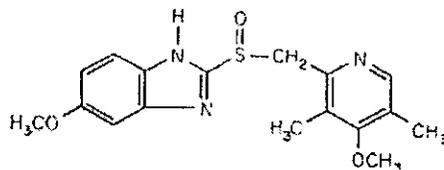
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**MOLECULAR WEIGHT:** 345.42

17. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
2	1			1	Inadequate	12/13/03	-----
3	3			4			

<sup>1</sup> Action codes for DMF Table:

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### B. Other Documents: None

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EES	Acceptable	11/14/03	S. Ferguson
Pharm/Tox	Not Applicable		
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Pending		
DMETS	pending		
EA	Not required*	3/5/04	M. Kowblansky
Microbiology	Not Applicable		

\*The applicant appropriately claims categorical exclusion on the basis that the concentration of the active moiety will not exceed 1 ppb at the point of entry into the aquatic environment

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# The Chemistry Review for NDA 21-372

The Executive Summary

**I. Recommendations**

- A. From the chemistry perspective, this application is Approvable, pending
  - 1. Resolution of the issues cited in the DR letter, the most notable of which are 1)  of the packet, 2) upgrade the drug substance impurity specifications to current FDA standards, and 3) add moisture, dissolution, and suspendibility testing to the drug product specifications.
  - 2. Resolution of the deficiencies in the drug substance DMF. The deficiencies have been communicated to the DMF holder.
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable** – No post-approval commitments are required at the present time.

**II. Summary of Chemistry Assessments**

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

The drug product is provided in single-use, child-resistant packets containing 20 mg of omeprazole USP, 1680 mg of sodium bicarbonate USP, flavors and other excipients. The packaging is designed to protect the product from moisture and light. Prior to administration, the contents of one packet are constituted with water . According to the applicant, the function of the sodium bicarbonate in this immediate release formulation is to protect the active ingredient from gastric degradation, by increasing the pH of the stomach. This distinguishes this proposed immediate release dosage form from the delayed release solid oral dosage forms of omeprazole currently on the market, which are enteric coated to prevent dissolution of the tablet in the stomach.

To ensure that the full 20 mg dose is administered to the patient, the applicant proposes to manufacture the product with  omeprazole in the formulation;  and to  packet with  of formulation .

. The data submitted with the application support the manufacture of the product with . However, the use  is not justified by the data; for the three commercial-size batches manufactured by the applicant, the data show that  omeprazole were recovered from the packet. The target fill weight should be lowered .

The applicant has appropriately requested an 18-month expiration period for the drug product, with controlled room temperature storage. The  stability data at controlled room temperature and  of accelerated stability data (40 degrees Centigrade) submitted with the application support this request. The data show no trends indicative of unusual instability, and suggest that with the submission of longer term stability data, expiration may be extended.

### Chemistry Assessment Section

The active drug substance is omeprazole, a racemic mixture of two enantiomers, which is also the active ingredient in a number of new and generic products currently on the market. Omeprazole is unstable under acidic conditions, but its stability increases with increasing pH. To provide fast dissolution in the stomach and enhanced bio-absorption, omeprazole is used in the formulation.

*NOTE: The applicant makes repeated references to a higher dose formulation containing 40 mg of omeprazole per packet. Since this NDA is for a single product that contains 20 mg of omeprazole per packet, the information regarding the higher dose formulation has not been carefully reviewed, but has been used as supporting information, where appropriate.*

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

The dosing instructions call for constituting the entire contents of the packet in 1-2 tablespoons of water, and drinking immediately. The instructions further direct to refill the container with water and drink. The label contains a cautionary statement not to substitute other liquids or foods for the water.

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

At this time, this application is judged to be Approvable based on the issues cited above (under Recommendations).

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemistry Reviewer: Marie Kowblansky, Ph.D.

ChemistryTeamLeader: Liang Zhou, Ph.D.

ProjectManager: Susan Daugherty

#### C. CC Block

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       § 552(b)(5) Draft Labeling

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Marie Kowblansky  
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Liang Zhou  
3/9/04 05:37:31 PM  
CHEMIST