

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-706

Chemistry Review(s)

ADDENDUM

FROM: Marie Kowblansky, Chemistry Reviewer

THROUGH: Liang Zhou, Chemistry Team Leader, HFD-180
Mary Lewis, Project manager, HFD-180

TO: NDA 21-706

In the final CMC review of this NDA, dated November 2, 2004, it was concluded that all CMC issues were resolved and that the NDA could be approved from a CMC perspective. An _____ expiration period was recommended at that time, based on real time stability data. There was a concern due to the appearance of a new unidentified impurity that increases at a faster rate than any of the known impurities. On further consideration, at _____ this unidentified impurity is present at a level of _____ well below the _____ ICH identification limit. In 24 months it is not likely that it will reach the _____ identification limit (which is the same as the specification limit for this impurity in the drug product). Consequently, the 24-month expiration period requested by the applicant is acceptable.

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/s/

Marie Kowblansky
11/29/04 01:44:21 PM
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Liang Zhou
11/29/04 02:06:49 PM
CHEMIST
Pending EER issues which need to be resolved.

11/2/04



CHEMISTRY REVIEW

NDA 21-706

ZEGERID
Omeprazole Powder for Oral Suspension
(40 mg single dose packets)

Santarus, Inc.

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

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B. Description of How the Drug Product is Intended to be Used 7

C. Basis for Approvability or Not-Approval Recommendation 7

At this time, this application is judged to be Approvable pending resolution of the issues cited above (under Recommendations). 7

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B. Endorsement Block 7

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-706
2. REVIEW #: 2
3. REVIEW DATE: November 2, 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

February 2, 2004

BC

July 23, 2004

BC

September 20, 2004

BC

September 27, 2004

BC

September 29, 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: Zegerid
- 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.

10. PHARMACOL. CATEGORY: Short-term treatment (4-8 weeks) of active benign gastric ulcer and —
of upper gastrointestinal bleeding in critically ill patients.

11. DOSAGE FORM: powder for oral suspension

CHEMISTRY REVIEW

Chemistry Review Data Sheet

12. **STRENGTH/POTENCY:** 40 mg per packet

13. **ROUTE OF ADMINISTRATION:** oral

14. **Rx/OTC DISPENSED:** Rx OTC

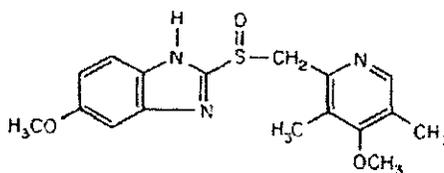
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

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: C₁₇H₁₉N₃O₃S

MOLECULAR WEIGHT: 345.42

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
| [3] | 1 | [] | Drug substance | 1 | Adequate | 4/20/04 | ----- |
| [] | 3 | [] | [] | 4 | | | |

¹ Action codes for DMF Table:

1 - DMF Reviewed.

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

2 - Type I 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:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 21-636 | <ul style="list-style-type: none"> 20 mg omeprazole powder for oral suspension. Application was approved 6/9/04 |
| IND | 46.656 | omeprazole powder for oral suspension |

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|----------------|----------|---------------|
| Biometrics | Not Applicable | | |
| EES | Pending | | |
| Pharm/Tox | Pending | | |
| Biopharm | Pending | | |
| LNC | Not Applicable | | |
| Methods Validation | Not required | | |
| DMETS | Pending | | |
| EA | Not required* | 11/04/04 | 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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CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review for NDA 21-706

Executive Summary

I. Recommendations

A. From the chemistry perspective, this application may be Approved with C expiration period pending

1. A recommendation from the Office of Compliance that the manufacturing facilities are Acceptable. (Inspections are scheduled to be completed November 11, 2004).
2. Satisfactory resolution of labeling issues, which are currently being negotiated with the applicant

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 40 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 in water

According to the applicant, omeprazole dissolves in the stomach and the function of the sodium bicarbonate is to protect the active ingredient from gastric degradation, by increasing the pH of the stomach. (The half-life of omeprazole is 10 minutes at pH 4 and 300 days at pH 11.) This distinguishes the proposed dosage form from the delayed release solid oral dosage forms of omeprazole currently on the market, which are enteric coated to prevent dissolution in the stomach. Although sodium bicarbonate in the amount present in this product can be administered therapeutically alone, without other active drug substances, a medical decision was made that in this product it would be treated as an excipient, i.e. the product would not be treated as a combination product. (See IND 46,656 May 13, 2003 meeting minutes and October 1, 2003 NDA 21-636 filing meeting minutes.) Considering the rapid degradation of omeprazole under acidic conditions, the fate of omeprazole in the stomach, when delivered in the proposed formulation, is not clear from the chemistry perspective. The medical consequences of this chemical uncertainty are under consideration by the pharmacology and medical disciplines.

To ensure that the full 40 mg dose is administered to the patient, the applicant proposes to

Data submitted with the application support

The applicant has requested a 24-month expiration period for the drug product, with room temperature storage. In support of this request, controlled room temperature stability data, 30°C stability data, and accelerated stability data (40°C) were submitted with the application. Although the data in general do not show trends indicative of unusual instability, an unexpected, unidentified degradation product that increases with storage

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

time and temperature has been observed. After [] at room temperature, it is the largest impurity present in the product; at [] it is significantly larger than any of the known, identified impurities. Since this impurity was present at a level as high as [] after only [] at 40°C, and [] after [] at 30°C, an [] expiration period, based on real-time data, is more appropriate at the present time than the extrapolated 24-month period proposed by the applicant.

Omeprazole, the active drug substance, is a racemic mixture of two enantiomers. It 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.

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 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 pending resolution of 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: Mary Lewis

C. CC Block

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1 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

Marie Kowblansky
11/5/04 10:29:16 AM
CHEMIST

Liang Zhou
11/5/04 01:53:41 PM
CHEMIST

10/15/04

CHEMISTRY REVIEW

NDA 21-706

ZEGERID
Omeprazole Powder for Oral Suspension
(40 mg single dose packets)

Santarus, Inc.

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

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1. A lowering of the specification limit to for the unidentified omeprazole-related impurity with the relative retention time of as determined by the HPLC method). Once the structure of this impurity has been ascertained, the limit requested by the applicant may be appropriate. 7

2. The addition of testing to the drug product specification. 7

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. 7

II. Summary of Chemistry Assessments.....7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

At this time, this application is judged to be Approvable based on the issues cited above (under Recommendations). 8

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A. Reviewer's Signature 8

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C. CC Block 8

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-706

2. REVIEW #: 1

3. REVIEW DATE: October 15, 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

February 2, 2004

BC

July 23, 2004

BC

September 20, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Santarus, Inc.

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Representative: Bonnie Hepburn, MD

Telephone: 858-314-5731

Fax: 858-314-5701

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zegerid
- 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.

10. PHARMACOL. CATEGORY: Short-term treatment (4-8 weeks) of active benign gastric ulcer and of upper gastrointestinal bleeding in critically ill patients.

11. DOSAGE FORM: powder for oral suspension

12. STRENGTH/POTENCY: 40 mg per packet

CHEMISTRY REVIEW

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

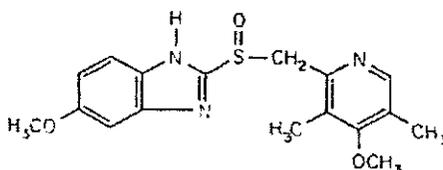
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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

MOLECULAR WEIGHT: 345.42

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CHEMISTRY REVIEW



Chemistry Review Data Sheet

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| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
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| Biometrics | Not Applicable | | |
| EES | Pending | | |
| Pharm/Tox | Pending | | |
| Biopharm | Pending | | |
| LNC | Not Applicable | | |
| Methods Validation | Not required | | |
| DMETS | Pending | | |
| EA | Not required* | 10/25/04 | 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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CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review for NDA 21-706

Executive Summary

I. Recommendations

A. From the chemistry perspective, this application is Approvable, pending

1. A lowering of the acceptance criterion for the unidentified omeprazole-related impurity with a relative retention time of — (as determined by the HPLC method) to —. Once the structure of this impurity has been ascertained, the . — limit requested by the applicant may be appropriate.
2. The addition of [] testing to the drug product specification.
4. Revision of the labeling as indicated in the Draft Discipline Review Letter (at conclusion of review).
5. Satisfactory completion of inspection of the manufacturing facilities.

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.

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Data submitted with the application support []

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

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C. Basis for Approvability or Not-Approval Recommendation

At this time, this application is judged to be Approvable pending resolution of 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: Mary Lewis

C. CC Block

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Marie Kowblansky
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Liang Zhou
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