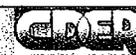
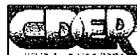


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-850

CHEMISTRY REVIEW(S)



*Review
#1*

NDA 21-850

Zegerid® Chewable Tablets

Santarus, Inc.

Raymond P. Frankewich, Ph.D.

**Office of New Drug Quality Assessment, Division of Post-
Marketing Assessment, Branch VIII**

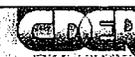


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Chemistry Review Data Sheet

1. NDA 21-850
2. REVIEW #1
3. REVIEW DATE: March 6, 2006
4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

NDA

May 25, 2005

Amendment

December 15, 2005

7. NAME & ADDRESS OF APPLICANT

Name: Santarus, Inc.

10590 West Ocean Air Drive

Address: Suite 200

San Diego, CA 92130-4682

Christine Simmons, PharmD

Representative: Vice President, Regulatory Affairs and Quality Assurance

Telephone: 858 - 314 - 5753

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- a) Proprietary Name: Zegerid®
b) Non-Proprietary Name (USAN): Omeprazole
c) Code Name/#: SAN-15, OME-IR(TAB)
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC 301 (FD&C Act) Sec. 505(b)(1)

10. PHARMACOL. CATEGORY: Proton pump inhibitor

11. DOSAGE FORM: Chewable tablet

12. STRENGTH/POTENCY: 20 mg, 40 mg

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:

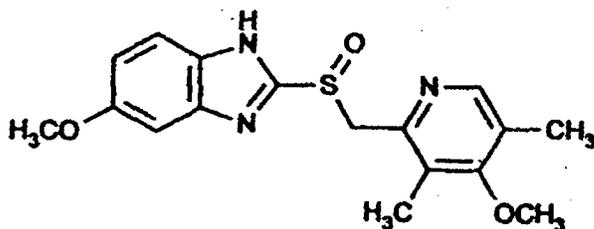
Chemical name: 1*H*-Benzimidazole, 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-;

Chemical formula: C₁₇H₁₉N₃O₃S

Molecular weight: 345.42

Structural formula:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	Adequate	3/06	Frankewich reviewed
/	IV	/	/	1	Adequate	3/06	"
/	IV	/	/	1	Adequate	3/06	"
/	III	/	/	3	Adequate	7/7/05	"
/	III	/	/	1	Adequate	2/06	"
/	III	/	/	3	Adequate	2/06	"

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: NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER
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CHEMISTRY REVIEW



Chemistry Review Data Sheet

REVIEWS			
Biometrics	NA	-	-
EES	Pending	1/27/06	Frankewich/ Janine M. D'Ambrogio (Compliance Coordinator)
Pharm/Tox	NA	-	-
Biopharm	Pending	1/27/06	Tien-Mein Chen, Ph.D.
LNC	NA	-	-
Methods Validation	To be requested, if appropriate	1/27/06	Frankewich
DMETS	Proprietary name acceptable, labeling revisions recommended	1/25/06	Tina Tezky, Pharm.D., Safety Evaluator
DDMAC	Proprietary name acceptable	1/25/06	Tina Tezky, Pharm.D., Safety Evaluator
EA	NA	-	-
Microbiology	NA	-	-

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 21-850

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC standpoint, this NDA is Approvable at this time. Clarification should be provided for the concerns listed in Part III of this review.

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

At this time, there are no requested postmarketing commitments, agreements and/or risk management steps. Clarification should be provided for the concerns listed in Part III of this review.

II. Summary of Chemistry Assessments

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

Regarding Drug Substance, reference is made to NDA 21-849 and to associated CMC Review (performed by Maria E. Ysern, MSc., Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment II, Branch III). NDA 21-849 was submitted for Zegerid® Capsules, 20 mg and 40 mg.

_____ omeprazole is supplied by _____. The manufacture and control of _____ omeprazole is provided in DMF _____, which has been reviewed and found to be adequate. Omeprazole is a racemic mixture of its two enantiomers.

The purpose of omeprazole is to inhibit the production of gastric acid. It accomplishes this by specific inhibition of the H⁺/K⁺ ATPase enzyme system, which exists at the surface of the gastric parietal cell, in the gastric mucosa. This enzyme system is responsible for acid production in the gastric mucosa. Omeprazole is said to block the final step of acid production.

Omeprazole is known to be highly unstable in acidic media (it has a half-life of less than 10 minutes at pH 4). Since the stomach is a highly acidic environment, any oral dosage form of omeprazole requires a component that will protect the active ingredient from acid degradation.

Omeprazole is the active ingredient in several products currently on the market. With the exception of Zegerid® Powder for Oral Suspension (NDA 21636 for 20 mg packet, NDA 21706 for 40 mg packet), which was approved in 2004, all of the omeprazole dosage forms marketed currently are delayed-release. All of them contain some kind of enteric coating that allows the omeprazole to pass through the stomach without being degraded. The disadvantage of enteric-coated omeprazole dosage forms is that their absorption is delayed (in the Pharmaceutical Development Section of the submission, the applicant indicates that



Executive Summary Section

the delay is 1.5 – 5 hours after the initial dose). The main purpose of this dosage form was to deliver the omeprazole more efficiently, while still protecting it from acid degradation.

The drug product is a chewable tablet, about 18 mm in diameter (about the size of a dime). It is required that chewable tablet dosage forms possess flavor and texture characteristics that will not interfere with the bioavailability of the active substance (in other words, it must taste good and be easy to swallow). This dosage form contains

See evaluation below of section 3.2.P.2 of the submission (Pharmaceutical Development of drug product) and section 3.2.P.8 (Stability of drug product) evaluated below.

The specific method of protecting the omeprazole from acid degradation used in this dosage form is through the use of large proportions of antacids. Sodium bicarbonate is about — (w/w) of the formulation; magnesium hydroxide is about — About — of the dosage form by weight, therefore, is made up of the antacids. The selection of these antacids, and their effectiveness in protecting the active ingredient, is discussed in the evaluation of section 3.2.P.2 of the submission (Pharmaceutical Development of drug product) and section 3.2.P.8 (Stability of drug product) evaluated below.

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

According to the package insert section of the labeling, the drug product (as well as Zegerid® Capsules and Zegerid® Powder for Oral Suspension) is indicated as follows:

- Duodenal Ulcers (20 mg once daily for 4 weeks);
- Benign Gastric Ulcer (40 mg once daily for 4 – 8 weeks);
- Symptomatic Gastroesophageal Reflux Disease (GERD) (20 mg once daily for up to 4 weeks);
- Erosive Esophagitis (EE) (20 mg once daily for 4 – 8 weeks);
- Maintenance of Healing of EE (20 mg once daily).

One additional indication is listed for the Oral Suspension ONLY: Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg initially, 40 mg 6 – 8 hrs. later and 40 mg daily thereafter for 14 days).

C. Basis for Approvability or Not-Approval Recommendation

Further clarification is needed for validation of analytical procedures, drug product stability commitment, and drug product stability testing.



III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

76 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/

Ray Frankewich
3/24/2006 10:21:17 AM
CHEMIST

Moo-Jhong Rhee
3/24/2006 10:48:22 AM
CHEMIST
Chief, Branch III