CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-456

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	022456
Applicant Name	Santarus Inc.
Date of Submission	Stamp Date: February 4, 2009
PDUFA Goal Date	December 4, 2009
Proprietary Name / Established (USAN) Name	Proprietary name has not been approved by DMEPA Omeprazole, sodium bicarbonate, magnesium hydroxide
Dosage Forms / Strength	Omeprazole/sodium bicarbonate/magnesium hydroxide tablets: 20 mg omeprazole/ 750 mg sodium bicarbonate / 343 mg magnesium hydroxide 40 mg omeprazole/ 750 mg sodium bicarbonate / 343 mg magnesium hydroxide
Proposed Indication(s)	20 mg once daily 1. Short-term treatment of active duodenal ulcer 2. Treatment of heartburn and other symptoms associated with GERD (gastroesophageal reflux disease) 3. Short-term treatment (4-8 weeks) of erosive esophagitis that has been diagnosed by endoscopy 4. Maintenance of healing of erosive esophagitis 40 mg once daily 1. Short-term treatment (4-8 weeks) of active benign gastric ulcer
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Erica Wynn, MD/ Ruyi He, MD
Pharmacology Toxicology Review	Sushanta Chakder, PhD
CMC Review	Tarun Mehta/ Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Jane Bai, PhD/Sue-Chih Lee, PhD
Biopharmaceutics Review	Patrick Marroum, PhD
DDMAC	Katie Klemm/Lisa Hubbard/Shefali Doshi/Robert Dean
DSI	Sripal Mada, PhD/Sean Kassim, Ph.D./C.T. Viswanathan, PhD
CDTL Review	Sue-Chih Lee, PhD
OSE/DMEPA	Kellie Taylor, PharmD, MPH/Denise Toyer, PharmD/Carol Holquist, RPh/Zachary Oleszczuk, Pharm D
SEALD	Debbie Beitzell, BSN

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

This NDA, submitted under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, seeks approval of omeprazole immediate release tablets containing sodium bicarbonate and magnesium hydroxide. There are two proposed omeprazole strengths, 20 and 40 mg. The sodium bicarbonate and magnesium hydroxide content is the same in each proposed omeprazole tablet strength (i.e., sodium bicarbonate 750 mg and magnesium hydroxide 343 mg per tablet). The reference listed drug product for this submission is Prilosec Delayed Release (DR).

The bridging pharmacokinetic study in this 505(b)(2) application was designed to demonstrate bioequivalence of the new 40 mg omeprazole/sodium bicarbonate/magnesium hydroxide product to the applicant's previously approved 40 mg strength Zegerid With Magnesium Hydroxide (IR) chewable tablet, which, like the proposed product, contains omeprazole, sodium bicarbonate and magnesium hydroxide (but with sodium bicarbonate and magnesium hydroxide content of 600 mg and 700 mg, respectively). The sodium bicarbonate and magnesium hydroxide in both products serve to protect the omeprazole from degradation by gastric acid. Marketed omeprazole delayed release products utilize enteric coatings to protect omeprazole from gastric acid.

Only the 40-mg strength of the new product was submitted in the initial submission of this NDA (022456); however the applicant amended the NDA on June 9, 2009, to seek approval of the additional lower strength, 20-mg. No bridging pharmacokinetic study was conducted for the 20-mg formulation because the Biopharmaceutics Team of ONDQA determined that there is no need for an additional bioequivalence PK study for the lower strength tablet based on proportional similarity to the 40 mg strength and the comparative dissolution profiles for the 20 mg and 40 mg strengths.

The proposed indications for the omeprazole/sodium bicarbonate/magnesium hydroxide 20 mg and 40 mg tablet are the same as the approved indications for the 20 mg and 40 mg Zegerid With Magnesium Hydroxide chewable tablet (NDA 21-850), which was approved March 24, 2006, but never marketed. The indications of the Zegerid With Magnesium Hydroxide chewable tablet are:

1) Duodenal Ulcer - short-term treatment of active duodenal ulcer. (20 mg)

2) Gastric Ulcer - short-term treatment (4-8 weeks) of active benign gastric ulcer.(40 mg)

3) Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) - treatment of heartburn and other symptoms associated with GERD. (20 mg)

4) Erosive Esophagitis - short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy. (20 mg)

5) Maintenance of Healing of Erosive Esophagitis (20 mg)

The chewable tablet comparator was approved under 505(b)(2) of the Federal Food, Drug and Cosmetic Act. NDA 21-850 was approved based on demonstration of bioequivalence of Zegerid With Magnesium Hydroxide 20 and 40 mg chewable tablets to Prilosec delayed release (DR) 20 and 40 mg capsule, respectively.

No review issues preclude approval. Although the Office of Compliance determined that the manufacturing controls for the drug substance component magnesium hydroxide were inadequate when the manufacturing facility was inspected and initially recommended Withhold approval on November 25, 2009, that recommendation was subsequently revised to "Acceptable" on December 2, 2009, after new information regarding the site was submitted and reviewed by the District Office.

2. Background

Omeprazole is a proton pump inhibitor that inhibits the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Omeprazole is acid labile and is degraded by gastric acid to a cationic sulfonamide. The omeprazole tablet proposed in this NDA is an "immediate-release" formulation that also contains sodium bicarbonate and magnesium hydroxide, which raise the gastric pH, protecting the omeprazole from acid degradation.

Dr. Sue-Chih Lee, the CDTL, has summarized the currently approved omeprazole products available by prescription in her review.

The Chemistry review for Zegerid Powder for Oral Suspension (NDA 021636) dated April 17, 2007, states that although sodium bicarbonate was not considered an active substance of the drug product when it was approved in June 2004, when later dosage forms of Zegerid were reviewed (NDA 021849 Zegerid Tablets and NDA 021850 Zegerid with Magnesium Hydroxide chewable tablets), the Agency determined that the sodium bicarbonate should be designated an active ingredient. The magnesium hydroxide in the Zegerid with Magnesium Hydroxide chewable tablet product was also determined to be an active ingredient, as documented in the Chemistry Review from NDA 021850, which states, "This decision means that the OTC antacids contained in this dosage form (sodium bicarbonate and magnesium hydroxide) are also considered active substances, in addition to omeprazole".

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. I concur with the CDTL, Dr. Lee, that the applicant 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 product." The Office of Compliance initially determined after the inspection of the manufacturing site for the drug substance magnesium hydroxide [redacted] that this site was not acceptable and recommended Withhold approval on November 25, 2009. The other manufacturing sites were found to be acceptable on inspection. On December 2, 2009, the "Withhold" recommendation was revised to "Acceptable", after new information regarding the site was submitted and reviewed by the District Office. I agree that in light of the revised status, the application can now be approved. b(4)

The composition of the omeprazole/sodium bicarbonate/magnesium hydroxide product proposed in this NDA is summarized in the table below.

Ingredient	Reference to Quality Standard	Manufacturer	Quantity (20 mg)	Quantity (40 mg)	Function
Omeprazole	USP	[redacted]			
Sodium Bicarbonate	USP	[redacted]	750 mg	750 mg	API and [redacted]
Magnesium Hydroxide [redacted]	GRAS	[redacted]			API and [redacted]
Hydroxypropyl Cellulose	NF	[redacted]			
Croscarmellose Sodium	NF	[redacted]			
Sodium Stearyl Fumarate	NF	[redacted]			
Total Weight/Unit			[redacted]	[redacted]	

b(4)

b(4)

The manufacturer of the magnesium hydroxide [redacted] is [redacted]
The manufacturing site is in [redacted]

Manufacturing Site:	Corporate Site:
[redacted]	[redacted]

b(4)

The CMC reviewer, Mr. Mehta, noted in his review that the applicant had investigated the root cause for increased levels of omeprazole impurity [redacted] in several lots of the finished drug product. The applicant determined that [redacted] b(4)

[redacted] Consequently, the manufacturing process and specification for magnesium hydroxide [redacted] were revised to limit the amount of [redacted] in b(4)

this material. ("The manufacturer will only use ——— magnesium hydroxide with —— that has —— levels below——— ') b(4)

The sodium bicarbonate drug substance is manufactured by a different manufacturer at a site in b(4)

Manufacturing Site:	Corporate Site:
[redacted]	[redacted]

b(4)

Mr. Mehta noted in his November 18, 2009 review that "While the applicant has not provided a DMF reference for this drug substance, according to 21CFR 314.50 (d)(1)(i), where requirements for drug substances are defined, reference to the current USP may satisfy these requirements. According to the Initial Quality Assessment by Marie Kowblanski, Ph.D., Pharmaceutical Assessment Lead, sodium bicarbonate is a well understood stable material, commonly used in pharmaceutical preparations, the brief manufacturing process description provided in the NDA, in conjunction with demonstrated conformance to USP requirements and an acceptable cGMP inspection will be sufficient to satisfy the requirements of 21CFR 314.50 (d)(1)(i), without the need for additional information in a DMF".

Mr. Mehta noted that the applicant listed the grade of the sodium bicarbonate used as USP—— b(4)
He commented that the USP monograph for sodium bicarbonate does not have a numerical modifier — He concluded that the——is "the supplier's designation for the USP grade sodium bicarbonate of a specific particle size range. This interpretation is supported in the description of the manufacturing process for sodium bicarbonate ——— [redacted] b(4)

The omeprazole manufacturer is ——— which is located in ——— The manufacturing facility is also located in ——— The reviewers noted in their review that omeprazole related substance degradants were adequately characterized. b(4)

Manufacture of the final drug product is accomplished by the following US sites:

Operation	Location	Drug Establishment #
Commercial Manufacturing and Packaging of Drug Product	Norwich Pharmaceuticals, Inc. (Referenced as NPI or Norwich) 6826 State Highway 12 North Norwich, NY 13814	1350044
[redacted]		

b(4)

The excipients are compendial grade chemicals that are not novel. The CMC reviewers determined that revised specifications submitted in an Amendment to the NDA on October 13, 2009 were adequate to monitor drug product quality "at the time of release and on stability".

The reviewers found that the stability data supported different expiration dating for the 40 mg tablets vs. the 20 mg tablets. Data supported an 18 months expiration date period for the 40 mg tablets. However, only a 9 month expiration date period could be supported for the 20 mg tablets based on the long term condition data submitted in the application. The reviewers noted that under accelerated conditions there were "significant changes" in the 20 mg product, and there were only 2 lots with sufficient data for appropriate statistical analysis. The applicant will continue ongoing stability studies for the registration lots of tablets.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted in this NDA. This is a 505(b)(2) application. I concur with the conclusions reached by the pharmacology reviewer, Dr. Chakder, that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with his labeling recommendations.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The Clinical Pharmacology reviewer, Jane Bai, PhD, concluded that the design of the pharmacokinetic bridging study [OME-IR (TAB)-C23] conducted to compare the new 40 mg omeprazole/sodium bicarbonate/magnesium hydroxide to the previously approved 40 mg Zegerid With Magnesium Hydroxide chewable tablet is acceptable. She determined that the comparative pharmacokinetic results for omeprazole showed that the two 40 mg tablet products are, in fact, bioequivalent.

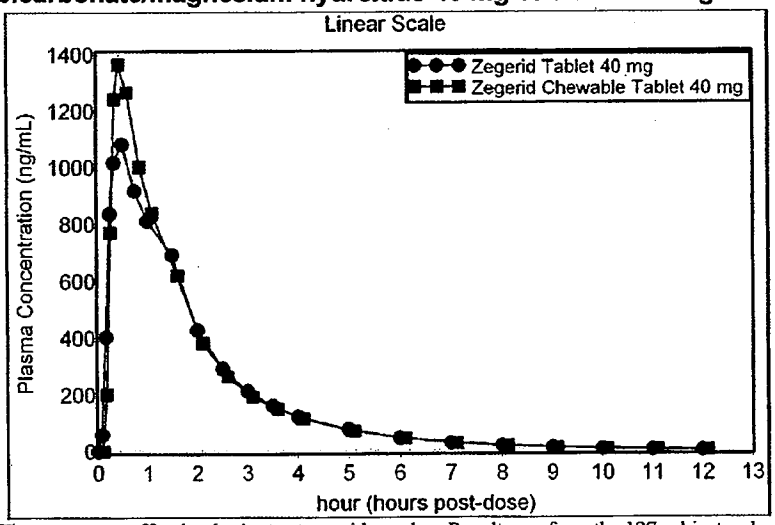
The pharmacokinetic bridging study was an open-label, randomized, 2-period crossover trial in which 127 individuals were evaluated. The results are summarized in the following table, which is reproduced from Dr. Lee's CDTL review (Table 1, with modified column headers):

PK comparison between the Omeprazole/sodium bicarbonate/magnesium hydroxide 40 mg tablets proposed for marketing and previously approved Zegerid With Magnesium Hydroxide chewable tablets, 40 mg

	Omeprazole/sodium hydroxide/magnesium hydroxide tablet (T)	Zegerid with Magnesium Chewable Tablet, 40 mg (R)	Geometric Mean ratio, % (T/R)	90% CI (%)
Ln(Cmax)	7.2 (0.55)	7.3 (0.54)	90.62	83.80-98.00
Ln(AUCt)	7.41 (0.73)	7.44 (0.74)	96.98	93.20-100.91
Ln(AUCinf)	7.41 (0.73)	7.44 (0.74)	96.98	93.19-100.94

The clinical pharmacology and clinical reviewers considered the possibility that a 505(b)(2) approval based on a comparison to another product approved under 505(b)(2) could result in a decrement in expected efficacy, secondary to "biocreep". The bioequivalence study submitted in this application shows that the new proposed omeprazole/sodium bicarbonate/magnesium hydroxide tablets meet the bioequivalence criteria required for approval, although the lower limit of the 90% confidence interval for the % Mean Ratio of Cmax approaches 80%, i.e. 83.8%. This is shown graphically below in the figure reproduced from Dr. Bai's Clinical Pharmacology Review (Figure 1 of her review). It should be noted that in the legend table within the figure "Zegerid Tablet" refers to the new omeprazole/sodium bicarbonate/magnesium hydroxide tablet proposed in the current NDA.

Mean Plasma Omeprazole Concentrations after Administration of Omeprazole/sodium bicarbonate/magnesium hydroxide 40 mg Tablets and Zegerid Chewable Tablets 40 mg



The curves are offset by 6 minutes to avoid overlap. Results are from the 127 subjects who completed all trial periods. Zegerid Tablet has been renamed as Zegerid [redacted] Tablet. b(4)

Dr. Bai noted that in the previous bioequivalence comparison of Zegerid With Magnesium Hydroxide chewable tablets to Prilosec DR 40 mg tablets, the Zegerid chewable tablets were found bioequivalent, and the lower bound of the 90% confidence intervals of the Cmax Mean Ratio, 118.8%, exceeded 100%. The lower bound for the 90% confidence interval for AUC also exceeded 100%. These results are summarized in the table below reproduced from Dr. Lee's CDTL review (Table 2):

Omeprazole PK comparisons between Zegerid With Magnesium Hydroxide Chewable Tablets 40 Mg and Prilosec DR 40 mg.

PK Parameter	Geometric Mean Ratio, % (Chewable/Prilosec DR)	90% CI (%)
Ln(Cmax)	129.96	118.83-142.12
Ln(AUCinf)	113.41	106.68-120.57

Dr. Bai had confidence that retention of efficacy of the new product could be assured, despite lack of direct comparison to Prilosec DR, based on her calculations of arithmetic mean ratios and cross study comparisons. I concur with the CDTL's conclusion (Dr. Sue-Chih Lee, PhD) that the proposed product would be expected to have efficacy similar to Prilosec DR based on cross study comparisons. She stated in her review, "By examining the bioequivalence study results comparing Zegerid with magnesium hydroxide chewable tablets to Prilosec Delayed Release capsules (Study TAB-C02), it is apparent that the proposed product would not be less effective than Prilosec Delayed Release capsules. This is because Zegerid With Magnesium Hydroxide chewable tablets had higher Cmax (ratio: 129.96%) and AUC (ratio: 113.41%) compared to Prilosec DR capsules."

In a memo dated August 10, 2009, Dr. Patrick Marroum, Biopharmaceutics reviewer, determined that the applicant's request for a biowaiver for the 20 mg strength tablet could be granted. He stated that the 20 mg strength tablet met the definition of proportionally similar and that the dissolution profiles in 3 media were comparable between the 20 mg and 40 mg strength tablets.

I concur with Dr. Bai's statement in her review that there were "no clinically meaningful differences in the number or nature of AEs (adverse events) reported in [the bioequivalence study submitted for review in this application] between the two trial products [the new omeprazole/sodium bicarbonate/magnesium hydroxide tablets and the previously approved Zegerid Chewable Tablets, 40 mg].

I concur with the Clinical Pharmacology reviewers' recommendations for labeling revisions, The product should be swallowed with water only.

6. Clinical Microbiology

Not applicable.

7. Clinical-Efficacy

There were no clinical trials conducted to evaluate efficacy and safety of the omeprazole product proposed under this 505(b)(2) NDA. The applicant is relying upon the FDA's previous findings of safety and efficacy for the reference product Prilosec DR capsules and the pharmacokinetic bridging study described in Section 5 Clinical Pharmacology/Biopharmaceutics. The clinical reviewers evaluated the proposed labeling and considered the safety and efficacy implications of the two additional active ingredients, sodium bicarbonate and magnesium hydroxide. These two additional active ingredients help protect the uncoated omeprazole from degradation by gastric acid, and are not themselves responsible for the clinical benefit associated with each of the product indications.

As discussed in Section 5 Clinical Pharmacology/Biopharmaceutics, the pharmacokinetic data submitted in this NDA establish that the proposed product is bioequivalent to the previously approved Zegerid With Magnesium Hydroxide chewable tablets. The previously approved Zegerid With Magnesium Hydroxide chewable tablets were previously shown to be bioequivalent to Prilosec DR, the reference listed drug for this 505(b)(2) NDA. The efficacy of these omeprazole products is expected to be comparable.

8. Safety

This is a 505(b)(2) application. Dr. Sue-Chih Lee, the CDTL, noted in her review that given that the bridging study submitted for review demonstrated that the proposed product is bioequivalent to the previously approved Zegerid with Magnesium Hydroxide Chewable tablets and "tended to have lower exposure compared to Zegerid with magnesium Hydroxide Chewable tablets", the proposed product is not expected to have a worse safety profile than the approved chewable tablet product.

Dr. Erica Wynn summarized the safety data submitted for review in this NDA. These data included post marketing safety information from the Santarus Adverse Event Reporting System (AERS) database for the previously approved Zegerid® formulations, publications from the medical literature regarding trials in which omeprazole in combination with sodium bicarbonate was studied, and adverse events from the pharmacokinetic trial comparing the proposed product with the previously approved chewable omeprazole/sodium bicarbonate/magnesium hydroxide tablets, OME-IR(TAB)-C23. Dr. Wynn also reviewed adverse event data from the open label safety trial [OMEIR(SUSP)-C07] of Zegerid® Suspension 40mg (omeprazole/sodium bicarbonate). The safety data from that study were previously reviewed under NDA 21-706, but were of interest to the primary reviewers of this NDA because the omeprazole exposure associated with the suspension is higher than the reference listed drug, Prilosec DR, and the Geometric Mean Ratios for the PK comparisons of the Zegerid With Magnesium Chewable Tablets to Prilosec DR exceeded 100% (but fell with bioequivalence criteria).

Dr. Wynn noted that 134 healthy subjects received at least one dose of a trial drug in the clinical trial data base. The pharmacokinetic study was a cross over trial and 132 received the proposed omeprazole/sodium bicarbonate/magnesium hydroxide tablets and 130 received the

Zegerid® Chewable tablet (omeprazole/sodium bicarbonate/magnesium hydroxide tablets). One hundred twenty-eight patients received both drugs. Thirty-one adverse events were reported by 26 patients in the trial. There were no deaths and no serious adverse events. The majority of adverse events were attributable to study procedures (i.e. venipuncture) and were considered unrelated to study drug. Dr. Wynn stated that the 11/31 adverse events that were considered possibly or probably related to study drug were consistent with currently labeled adverse event information in the approved Zegerid products. The events included nausea, abdominal pain and headache. Two patients who had elevated bilirubin, AST, or ALT during the study had documented normalization of these values within 10 days.

Dr. Wynn evaluated the safety data from the Zegerid Suspension 40 mg safety study, OME-IR(SUSP)-C07, and concluded that the safety profile observed in that previously reviewed study was similar to the adverse event profile found in the Prilosec label. She also concluded that the post-marketing safety data for the Zegerid products "appear to present a safety profile similar to that of the approved omeprazole labeling."

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product does not contain a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

The applicant requested a full waiver for all pediatric age groups. Pediatric studies were not conducted or requested with the approval of Zegerid® with Magnesium Hydroxide chewable tablets (NDA 21-850). Prilosec DR is approved for the treatment of GERD and maintenance of healing of erosive esophagitis in pediatric patients. The reviewers concurred with waiving the pediatric study requirement for this application for the following reasons listed in Dr. Lee's CDTL review:

(1) For the duodenal and gastric ulcer indications, trials would be highly impractical because the number of pediatric patients with the condition is small.

(2) For the GERD and maintenance of healing of erosive esophagitis indications, additional studies using the proposed formulation will not offer therapeutic benefit over existing omeprazole delayed release formulations. Currently, Prilosec is approved for use in pediatric patients as young as one year of age. For the 1- to 11-month-old age group, further clinical understanding of the disease process and diagnosis is needed to determine the proper study design and efficacy endpoint(s).

The Pediatric Review Committee concurred with waiving the pediatric study requirement for this application. The final decision to waive the pediatric study requirement for this application was based on:

1) For the indications of short-term treatment of active duodenal ulcer and short-term treatment (4 to 8 weeks) of active benign gastric ulcer, we are waiving the pediatric

study requirement because the necessary studies are impossible or highly impracticable.

2) For the indications of treatment of heartburn and other symptoms associated with GERD, short-term treatment (4 to 8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and maintenance of healing of erosive esophagitis, we are waiving the pediatric study requirement for ages birth to 1 month because the necessary studies are impossible or highly impracticable; additionally we are waiving the pediatric study requirements for age 1 month to 16 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

Section 8.4 Pediatric Use of the product label will state "The safety and effectiveness of Omeprazole/Sodium Bicarbonate/Magnesium Hydroxide Tablets in pediatric patients less than 18 years of age have not been established".

11. Other Relevant Regulatory Issues

Dr. Erica Wynn noted in her review that the applicant submitted an FDA form 3454 certifying that it had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. The applicant certified that each investigator disclosed no proprietary interest in the product or significant equity in the applicant, and that no investigator was the recipient of significant payments of other sorts.

The DSI report for the bridging study stated that "Following the above inspections, DSI concludes that clinical and analytical data from OME-IR (TAB) -C23 are acceptable for the review." This conclusion was confirmed in a DSI addendum report dated November 10, 2009.

The proposed product is a combination drug product. The role of the active ingredients sodium bicarbonate and magnesium hydroxide is to raise gastric pH to protect the omeprazole from degradation by gastric acid. In her CDTL review, Dr. Lee summarized the regulatory history of how the combination product issue was addressed in the prior product approvals [NDA 21-849 [redacted], and NDA 21-850 (Zegerid with magnesium hydroxide chewable tablets)]. She noted that Dr. Joyce Korvick addressed the combination drug product issue for these products in her memos dated February 17, 2006 and February 22, 2006, and states that the same reasoning applies to this application. "Specifically, this is considered a special case covered in 21 CFR 300.50 (a)(1) 'Special cases of this general rule are where a component is added to enhance the safety or effectiveness of the principal active component.'" Dr. Korvick's February 17, 2006 review points out that omeprazole is dosed once daily for the approved indications of the Zegerid products, and that "while patients might experience a short period of heart burn relief due to the sodium bicarbonate, sodium bicarbonate taken in this dose once per day is not an effective treatment for GERD and erosive esophagitis." This also applies to the magnesium hydroxide component of the product proposed in the current NDA.

b(4)

12. Labeling

The applicant proposed to market the omeprazole/sodium bicarbonate/magnesium hydroxide product that is the subject of this NDA with the name "ZEGERID", which is the same name of products currently marketed by the applicant that contain omeprazole and sodium bicarbonate, but no magnesium hydroxide. DMEPA informed the applicant that the name "ZEGERID" could not be used for the omeprazole/sodium bicarbonate/magnesium hydroxide product, because of the difference in active ingredients from currently marketed products named "ZEGERID" (the capsule and suspension products). In a letter to the applicant, DMEPA stated that "Thus, the proposed product is a different drug product than the currently market Zegerid products and the proposed product should be marketed under a separate proprietary name."

The applicant submitted a new name for review, "ZEGERID——," which differed only by the addition of a modifier. DMEPA reviewed this name and found it unacceptable. The DMEPA reviewers found the modifier "—— did not clearly convey its intended meaning, i.e. that the product contains an additional active ingredient, magnesium hydroxide. They also found that the name was vulnerable to name confusion with Zegerid, because of the orthographic and phonetic similarities; in addition to overlapping product characteristics. The Division of Drug Marketing, Advertising and Communications (DDMAC) found the name ZEGERID—— unacceptable from a promotional perspective. The applicant was informed that the second name reviewed was not acceptable. By the time of the approval action of this NDA the applicant did not have an approved tradename for this omeprazole/sodium bicarbonate/magnesium hydroxide product. b(4) b(4)

In an additional labeling review, the DMEPA reviewers recommended that the 3 names of the active ingredients be separated by commas, instead of forward slashes (/). The CMC review team did not concur with this recommendation because there will be no trade names associated with this product (because no trade name has been approved) and the use of commas suggests presence of multiple tablets. The clinical team concurred with the CMC review team's concerns. I concur with their final decision to maintain the forward slashes, since there will be no approved trade name at the time of the NDA approval. When the applicant has proposed a trade name that can be approved, we can reconsider the use of commas vs. forward slashes between the names of the active ingredients in product labeling.

The DMEPA reviewers also recommended that the established name presentation on the container labels should be revised to keep the words "sodium" and "bicarbonate" together on the same line. The clinical reviewers considered this recommendation, and ultimately agreed. The applicant was contacted to modify the established name presentation.

The Clinical Reviewer, Dr. Erica Wynn, carefully reviewed the proposed label and made a number of recommendations for revisions. She was particularly attentive to clinical situations in which patients should avoid or minimize use of the sodium bicarbonate or magnesium active ingredients of this product. Her recommendations included:

1) Omeprazole/sodium bicarbonate/magnesium hydroxide tablets should be

contraindicated in patients with known hypersensitivity to the drug or any of its components and in patients who can not take magnesium. (The label was so revised.)

2) Under "Warnings and Precautions," add "Sodium content should be taken into consideration when administering to patients on a sodium-restricted diet or patients who are at risk of developing congestive heart failure." (This change was incorporated in the final label.)

3) Under "Warnings and Precautions," add metabolic alkalosis and hypocalcemia to the list of conditions in which the drug should be used with caution. (This change was incorporated in the final label, under 5.3 Buffer Content [redacted] b(4)

4) Under Section 6.2 Post-Marketing Experience, remove "Gastroduodenal carcinoids have been reported inpatients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, " because it may encourage the use of the drug for Zollinger Ellison. (This change was not adopted because it provides safety information and the review team did not concur that it would encourage off label use for Zollinger Ellison.)

5) Under Section 8.4, include a statement that there were no adequate and well controlled studies in pediatric patients. (The final negotiated label will state that the safety and effectiveness of the product in pediatric patients less than 18 years of age have not been established.)

6) Under Section 17 Patient Counseling, include the statement, "Patients should be instructed to not substitute two 20 mg tablets for one 40 mg tablet because the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg). This would result in the patient receiving twice as much sodium bicarbonate and magnesium hydroxide." (This recommendation was incorporated in the label.)

DMEPA reviewer, Zachary Oleszczk recommended changes to the container labeling to reduce the risk of medication errors, which were accepted by the applicant, who submitted revised container labeling. These changes included changing the color scheme to differentiate the two tablet strengths and adding a statement to the container label that two 20 mg tablets should not be substituted for one 40 mg tablet, since both omeprazole strength tablets contain the same amount of sodium bicarbonate and magnesium hydroxide).

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval.

- Risk Benefit Assessment – I concur with the CDTL that the proposed product has the same favorable risk and benefit characteristics as the currently marketed omeprazole products for the same indications, based on the bioequivalence established in the pharmacokinetic bridging study submitted in this application.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  None. For the indications of short-term treatment of active duodenal ulcer and short-term treatment (4 to 8 weeks) of active benign gastric ulcer, we are waiving the pediatric study requirement because the necessary studies are impossible or highly impracticable.

  For the indications of treatment of heartburn and other symptoms associated with GERD, short-term treatment (4 to 8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and maintenance of healing of erosive esophagitis, we are waiving the pediatric study requirement for ages birth to 1 month because the necessary studies are impossible or highly impracticable; additionally we are waiving the pediatric study requirements for age 1 month to 16 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

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

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/s/

DONNA J GRIEBEL
12/04/2009