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APPLICATION NUMBER:

22-456

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 3, 2009
From	Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP III
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-456
Applicant	Santarus, Inc.
Date of Submission	January 28, 2009; Received February 4, 2009
PDUFA Goal Date	December 4, 2009
Proprietary Name / Established (USAN) names	No proprietary name at this time Omeprazole/sodium bicarbonate/magnesium hydroxide
Dosage forms / Strength	Omeprazole/sodium bicarbonate/magnesium hydroxide tablets, 20 mg/750 mg/343 mg and 40 mg/750 mg/343 mg
Proposed Indication and Dosing Regimen	***20 mg once daily in adults*** • Short term treatment of active duodenal ulcer • Treatment of heartburn and other symptoms associated with GERD • Short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy • Maintenance of healing of erosive esophagitis ***40 mg once daily in adults*** • Short term (4-8 weeks) treatment of active benign gastric ulcer
Recommended Action:	Approval under 21 CFR 314

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1. Introduction

This submission, received February 4, 2009, is the original New Drug Application (NDA) for Omeprazole/sodium bicarbonate/magnesium hydroxide tablets. This drug product is intended for treatment of active duodenal ulcer, active benign gastric ulcer, heartburn and other symptoms associated with GERD, and erosive esophagitis as well as for maintenance of healing of erosive esophagitis. The primary emphasis of this memorandum is on the issues discussed during the review.

2. Background

Omeprazole/sodium bicarbonate/magnesium hydroxide tablet is an immediate release drug product containing a proton pump inhibitor (omeprazole) and two antacids (sodium bicarbonate and magnesium hydroxide). Omeprazole suppresses gastric acid secretion by irreversibly binding to the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Therefore, gastric acid suppression lasts much longer than the short plasma half-life of omeprazole (around 1 hr in extensive metabolizers) would suggest, allowing once daily dosing. The acid suppression effect leads to inhibition of both basal and stimulated acid secretion. Omeprazole does not exhibit anticholinergic or H2 histamine antagonistic properties.

Chemically, omeprazole is acid labile and is rapidly degraded by gastric acid. To minimize degradation of omeprazole in the acidic environment of the stomach, some approved omeprazole products are designed as delayed release formulations. An alternative way of protecting omeprazole from stomach acid is by adding antacid(s) in the formulation to raise gastric pH, thus making it possible to formulate omeprazole in immediate release formulations. The subject drug product obviously belongs to the latter category.

This drug product is manufactured in two strengths of omeprazole, 20 mg and 40 mg. For either strength, the antacid content is the same (i.e., sodium bicarbonate 750 mg and magnesium hydroxide 343 mg per tablet) so that the two strengths have the same acid neutralizing capacity in the stomach.

The indications and dosing regimes proposed for the subject product are the same as those for Zegerid with Magnesium Hydroxide Chewable Tablets. The 20 mg (in terms of omeprazole) once daily regimen is recommended for all the indications sought by the sponsor, except for the treatment of active benign gastric ulcer, which has a recommended dosing regimen of 40 mg once daily. Note that the sponsor is not pursuing an indication for pathological hypersecretory conditions (an indication for Prilosec) nor for reduction of risk of upper gastrointestinal bleeding in critically ill patients (an indication for Zegerid Powder for Oral Suspension).

2.1 Regulatory History

2.1.1 Products

Below is a list of omeprazole prescription (Rx) drug products approved in the US.

Prilosec/AstraZeneca:

- NDA 19-810: Prilosec capsules with delayed release pellets (omeprazole, 10 mg, 20 mg, 40 mg); approved 1989-1998 (generic drugs available)
- NDA 22-056: Prilosec delayed release for suspension (omeprazole magnesium, 2.5 mg or 10 mg per packet); approved in 2008

Zegerid/Santarus:

- NDA 21-636: Zegerid powder for oral suspension (omeprazole 20 mg or 40 mg /sodium bicarbonate 1.68g per packet); approved in 2004
- NDA 21-849: Zegerid capsules (omeprazole 20 mg or 40 mg /sodium bicarbonate 1.1g); approved in 2006
- NDA 21-850: Zegerid with magnesium hydroxide chewable tablets (Omeprazole 20 mg or 40 mg /sodium bicarbonate 600 mg /magnesium hydroxide 700 mg); approved in 2006

2.1.2 Regulatory history of omeprazole/sodium bicarbonate/magnesium hydroxide tablets

Two meetings were held between the sponsor and the Agency during the development of the product. The sponsor requested under NDA 21-850 (for Zegerid with magnesium hydroxide chewable tablets) a Type B meeting with the Agency to discuss the development of the subject swallowable tablets of omeprazole/sodium bicarbonate/magnesium hydroxide. A meeting was held on April 8, 2008, in which CMC, Biopharmaceutics and regulatory issues were discussed. In the meeting, the Agency indicated that we would clarify whether the new product could be filed under NDA 21-850 as a supplement. The second, pre-NDA meeting occurred September 9, 2009, under IND 75,432, in which stability data, product specifications and NDA submission were discussed.

2.2 Current Submission

This is a 505(b)(2) application seeking approval of the immediate release tablets containing omeprazole (20 mg or 40 mg) in combination with sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg). These tablets are hereafter referred to as the proposed products.

The January 28, 2009 submission contained information on the 40mg strength only. On June 9, 2009, the sponsor submitted an amendment seeking approval of an additional dosage strength of 20 mg. There are no safety and efficacy trials conducted specifically to support the approval of the proposed products. Provided in the submission is a pivotal, single dose,

randomized, crossover, bioequivalence study (OME-IR (TAB)-C23) of omeprazole administered as the proposed product (40 mg strength) and Zegerid with magnesium hydroxide chewable tablets 40 mg in healthy subjects. In addition, several supporting pharmacokinetic (PK) and pharmacodynamic (PD) studies previously used to support other NDAs are also included in the submission. Overall, the studies submitted in the application are as follows:

- A single-dose PK study comparing the proposed product 40 mg and Zegerid with magnesium hydroxide chewable tablets 40 mg (Study TAB-C23).
- Two single- and multiple-dose PK/PD studies comparing Zegerid with magnesium hydroxide chewable tablets 20 mg and 40 mg and Prilosec delayed release capsules 20 mg and 40 mg (Study TAB-C01 and TAB-C02).
- Two single- and multiple-dose PK/PD studies comparing Zegerid Suspension 20 mg and 40 mg and Prilosec delayed release capsules 20 mg and 40 mg (Study SUSP-C06 and SUSP-C02).
- An open-label safety trial of Zegerid Suspension 40 mg (SUSP-C07).
- Postmarketing safety information from the Santarus Oracle Adverse Event Reporting System (AERS) database for Zegerid.

There are no in vivo bridging studies for the 20 mg strength. The ONDQA Biopharm Team found this acceptable as biowaiver can be granted to the lower strength based on the following:

(1) The formulation for the 20 mg strength is proportionally similar to that of the higher strength (40 mg).

(2) The comparative dissolution profiles for the 20 mg and 40 mg strengths met the criteria for similarity.

This determination was documented in a memo by Dr. Patrick Marroum of ONDQA dated August 10, 2009.

No pediatric studies were conducted using the proposed products. The sponsor requested full waiver of pediatric studies for all indications.

Reference products

Prilosec® Delayed-Release Capsules (AstraZeneca / NDA 19-810)
To support the proposed product, the sponsor is relying on Agency's previous finding of safety and efficacy for Prilosec Delayed-Release Capsules, 20 mg and 40 mg.

Zegerid with Magnesium Hydroxide Chewable Tablets (Santarus/NDA 21-850)
For NDA 22-456, the sponsor conducted a bridging PK bioequivalence study comparing the 40 mg proposed product to the 40 mg Zegerid with Magnesium Hydroxide Chewable Tablets. To address the bio-creep issue, data from NDA 21-850 was used to link the proposed product to Prilosec Delayed-Release Capsules (see also Section 5: Clinical Pharmacology).

2.3 NDA Review Documents

All review disciplines participating in the review of this NDA have provided written review documents, which are listed below:

- Clinical Pharmacology Review by Jane Bai, dated November 2, 2009
- Clinical Review by Erica L. Wynn, dated October 30, 2009
- Nonclinical Review by Sushanta Chakder, dated October 28, 2009
- CMC reviews by Tarun Mehta, dated November 18 and December 3, 2009
- DMEPA Reviews by Zachary Oleszczak:
  - Proprietary Name Reviews dated November 17, 2009
  - Labeling Reviews dated November 5 and December 2, 2009
- DDMAC Labeling Review by Katie Klemm dated October 23, 2009
- SEALD Labeling Review by Debra C. Beitzell, dated October 28, 2009

The above reviews should be consulted for further details of the application. This memorandum summarizes selected information from these review documents, with primary emphasis on the issues discussed during the review process.

3. CMC

The reader is referred to the CMC Review by Tarun Mehta dated November 18, 2009 for detailed information.

3.1 Review Summary

Overview of Drug Substance:

The proposed tablet 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)

The inspection by the Office of Compliance of the manufacturing facility for magnesium hydroxide [redacted] found deficiencies which were considered approval issues. On December 2, 2009, an email from Marie Kowblansky of ONDQA indicated that the Office of Compliance now finds the site acceptable. b(4)

Overview of Drug Product:
The proposed drug product contains omeprazole 20 mg or 40 mg, sodium bicarbonate 750 mg and magnesium hydroxide 343 mg (equivalent to [redacted] of magnesium hydroxide [redacted]. 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 [redacted] bottle of 30 tablets for commercial use or [redacted] The container/closure system is a HDPE bottle with [redacted] with [redacted] b(4) 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 approved drug products at or below the proposed concentration. The drug product is manufactured by [redacted] 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 [redacted] ([redacted] omeprazole. b(4)

The identity, strength, purity and quality of the final drug product are assured by the specifications: appearance, ID, content uniformity, weight variation, assay of APIs and related substances, dissolution, [redacted] and acid neutralization capacity. Based on available stability data, the expiration dating period of 18 months is granted for the 40-mg tablets and nine (9) months for the 20-mg tablets. b(4)

3.2 Final 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. The Office of Compliance has now found the manufacturing facility for magnesium hydroxide [redacted] acceptable. b(4)

Therefore, the application is acceptable from the CMC perspective.

4. Nonclinical Pharmacology/Toxicology

4.1 Review Summary

There were no new nonclinical pharmacology/toxicology data in the submission, and no additional review of nonclinical data was performed in this review cycle. The nonclinical Pharmacology/Toxicology review focused on labeling. The recommendations for labeling revisions have been negotiated with the Applicant during the review cycle. The labeling revisions included changes to the Pregnancy section, the Labor and Delivery section, the

Carcinogenesis, Mutagenesis and Impairment of Fertility section and the Animal Toxicology and/or Pharmacology section.

For details, please refer to the review by Sushanta Chakder, dated October 28, 2009.

4.2 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline.

5. Clinical Pharmacology

5.1 Review Summary

Clinical pharmacology data were reviewed by the Clinical Pharmacology reviewer, Jane Bai, and summarized below. Please refer to the Clinical Pharmacology Review dated November 2, 2009, for more information.

The bridging study (OME-IR (TAB)-C23) was an open-label, randomized, 2-period crossover study in 127 healthy subjects to determine whether the proposed product (40 mg strength) is bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg. In each period, subjects received a single dose of the proposed product or Zegerid chewable tablets, administered with 120 mL of water 1 hour prior to beginning a standardized high-fat breakfast after an overnight fast. The washout period was 7 days. The to-be-marketed formulation for the proposed product was used in this study. The comparative omeprazole PK results show that the proposed product (40mg) is bioequivalent to Zegerid with magnesium hydroxide chewable tablets 40 mg. This is evidenced by the 90% confidence interval (90%CI) for the geometric mean ratio for both Cmax and AUC being within the 80-125% range (see Table 1).

Table 1: PK comparison between the proposed product (40mg) and Zegerid with Magnesium Hydroxide Chewable Tablets 40 mg

PK Parameter	Proposed product (T)	Zegerid with Magnesium hydroxide (R)	Geometric mean ratio, % (T/R)	90% CI (%)
Ln(Cmax)	7.20 (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 DSI report dated July 8, 2009, by Sripal R. Mada of the Division of Scientific Investigations stated that "Following the above inspections, DSI concludes that clinical and analytical data from OME-IR (TAB) -C23 are acceptable for the review." The addendum dated November 10, 2009, by Sripal R. Mada and Sean Y. Kassim of DSI upheld this determination.

Bio-creep issue: For this application, the sponsor is relying on the Agency's previous finding of safety and efficacy for Zegerid with magnesium hydroxide chewable tablets and Prilosec

delayed release capsules. Since the proposed product tends to be somewhat lower in PK parameters compared to Zegerid with magnesium hydroxide chewable tablets, which was approved via 505(b)(2) without clinical safety and efficacy data, the concern is whether there is bio-creep that represents a lack of efficacy in the proposed product. 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. Thus, through cross-study comparisons with a common product in each study, one finds the exposure for the proposed product greater than that for Prilosec DR capsules. As such, biocreep is a non-issue and the proposed product is expected to have similar efficacy to Prilosec DR capsules.

Table 2: PK comparison between Zegerid with Magnesium Hydroxide Chewable Tablets 40 mg and Prilosec Delayed Release Capsules 40 mg

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

5.2 Final Recommendation

The application is acceptable from the Clinical Pharmacology perspective.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because the proposed product is not an antimicrobial agent.

7. Clinical/Statistical- Efficacy

7.1 Review Summary

There are no dedicated efficacy trials for the proposed product and no statistical review has been conducted for this NDA. The efficacy of the proposed product is inferred from two bioequivalence studies: (1) the study comparing the proposed product to Zegerid Chewable Tablets (Study OME-IR (TAB)-C23) and (2) the study comparing Zegerid Chewable Tablets to Prilosec Delayed Release Capsules (Study TAB-C02). The reader is referred to Section 5 above, the Clinical Pharmacology Review dated November 2, 2009, and the Clinical Review by Erica L. Wynn dated October 30, 2009 for more information.

7.2 Final Recommendation

An Approval Action is the final recommendation from a Clinical Efficacy standpoint.

8. Safety

8.1 Review Summary

The following safety information is excerpted from the Clinical Pharmacology review by Jane Bai dated November 2, 2009, the Clinical Review by Erica L. Wynn dated October 30, 2009 and the Clinical Team Leader Review by Ruyi He dated November 10, 2009.

The proposed product vs. Zegerid with Magnesium Hydroxide Chewable tablets:
Study OME-IR (TAB)-C23 showed that the proposed product tended to have lower exposure compared to Zegerid with Magnesium Hydroxide Chewable tablets although it still met the bioequivalence criteria. As such, the proposed product is not expected to have poorer safety profile than Zegerid with Magnesium Hydroxide Chewable tablets. In addition, in this bioequivalence trial in 132 healthy adult volunteers, the safety profile of the proposed product did not differ from that of Zegerid with Magnesium Hydroxide Chewable Tablets.

Zegerid with Magnesium Hydroxide Chewable tablets vs. Prilosec Delayed Release capsules: In two PK/PD bioequivalence trials, Zegerid Chewable Tablets were equivalent to Prilosec Delayed-Release capsules with respect to total systemic omeprazole exposure [AUC(0-inf)] at both 20-mg and 40-mg dosage strengths after a single dose and at steady state. As anticipated when comparing an immediate-release and a delayed-release formulation, peak exposure (Cmax) was higher for Zegerid Chewable Tablets than for Prilosec in these trials. However, the safety profile of Zegerid Chewable Tablets was no different from that described in the Prilosec label and is consistent with the safety profile of other Zegerid formulations.

Zegerid Powder for Suspension vs. Prilosec Delayed Release capsules: In two PK/PD bioequivalence trials, Zegerid Suspension was equivalent to Prilosec Delayed Release capsules with respect to AUC(0-inf) at both 20-mg and 40-mg dosage strengths, after a single dose and at steady state. Again, as anticipated when comparing an immediate-release and a delayed-release formulation, Cmax was higher for Zegerid Oral Suspension than for Prilosec in these trials. However, the safety profile of Zegerid Oral Suspension was no different from that described in the Prilosec label. Additionally, an open-label safety trial showed that once-daily administration of Zegerid Suspension 40 mg did not have safety concerns associated with the higher Cmax of Zegerid Suspension 40 mg. Based on the postmarketing adverse event data for Zegerid collected since approval of the first formulation in June 2004, no new safety issues have been identified.

Conclusion regarding safety of the proposed product:
The above observations generally support the safety of the proposed products as related to the systemic exposure of omeprazole.

Additional safety considerations: Because the proposed products contain 750 mg of Sodium Bicarbonate and 343 mg of Magnesium Hydroxide, precautionary information regarding the

sodium bicarbonate and magnesium hydroxide should be included in the labeling. For detailed safety evaluation of this NDA, please refer to Dr. Erica Wynn's review.

8.2 Final Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The sponsor did not conduct any studies in pediatric patients using the proposed products and requested a full waiver of pediatric studies for all the indications. We agree to grant a waiver of pediatric studies as explained in Section 13.4. The Pediatric Review Committee concurred with waiving the pediatric study requirement for this application.

11. Other Relevant Regulatory Issues

11.1 Division of Scientific Investigations (DSI)/Office of Compliance audits

The clinical and analytical sites for the pivotal bioequivalence study [study OME-IR (TAB)-C23] were audited by DSI. The DSI report dated July 8, 2009, by Sripal R. Mada of DSI stated that "Following the above inspections, DSI concludes that clinical and analytical data from OME-IR (TAB) -C23 are acceptable for the review." The addendum dated November 10, 2009, by Sripal R. Mada and Sean Y. Kassim of DSI upheld this determination.

A separate inspection of the manufacturing facilities for the drug substances found deficiencies with [redacted], the supplier of magnesium hydroxide. The Office of Compliance recommended against approval of this application until December 2, 2009, when the site was considered acceptable. b(4)

11.2 Combination drug products

The proposed product is considered a combination drug product. Both sodium bicarbonate and magnesium hydroxide raise gastric pH after oral administration of the product. However, the primary function of these two components are to minimize degradation of omeprazole (the active moiety) by the stomach acid. For the approval of NDA 21-849 [redacted] and NDA 21-850 (Zegerid with magnesium hydroxide chewable tablets), Dr. Joyce Korvick addressed the combination drug product issue in her b(4)

memos dated February 17 and 22, 2006, respectively. The same reasoning applies to the proposed product. 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."

12. Labeling

12.1 Proprietary name

Proprietary name denied (The sponsor has no trade name for the product at this time):
The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed name "Zegerid ——" not acceptable because the stand alone modifier "——" is ambiguous as to its intended meaning. In a study involving 150 participants, a majority of respondents (n=80) stated that the word "——" had no associated meaning or that the modifier "——" was associated with a variety of meanings including extra benefit, extra strength, large amount of ingredient, strength, effective, combination product, extended release, or new formulation. Sixty-nine of the 150 participants stated that the word "——" was associated with an additional active ingredient. However, these responses did not specify that the additional active ingredient was magnesium hydroxide. Moreover 54% (n=80) of the combined respondents indicated either no association or a meaning other than an additional active ingredient. The proposed proprietary name, Zegerid ——, was also found to be orthographically and phonetically similar to; and have overlapping product characteristics with the sponsor's currently marketed product Zegerid. DMEPA issued a letter dated November 19, 2009, to the sponsor denying their proposed Proprietary Name of Zegerid ——. At this time, the sponsor does not have a proprietary name for the product. b(4) b(4) b(4) b(4) b(4)

12.2 Labeling Comments

The sponsor was requested to revise the package insert labeling and container labeling. The main issues discussed are listed below. There were also internal discussions on what should go to the "Patient Counseling Information" section. Agreements between the sponsor and the Agency have been reached at this time.

Physician Labeling:
1. As indicated in their review dated December 2, 2009, DMEPA recommends that the established name be presented as "Omeprazole, Sodium Bicarbonate, and Magnesium Hydroxide Tablets" but defers to the Division of Gastroenterology Products' assessment of the final presentation. This matter was discussed earlier among the review team members. It was decided that this presentation, although consistent with the USP presentation for combination products, can be confusing as it reads like three separate tablets. Therefore, we keep the established name of the proposed drug product as shown below:

Omeprazole/Sodium Bicarbonate/Magnesium Hydroxide

2. Both the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg). It is important to indicate that two 20 mg tablets are not equivalent to and should not substitute for one 40 mg tablet.

3. Because the formulation contains sodium bicarbonate, the drug should be used with caution in patients on a sodium restricted diet and those at risk of developing congestive heart failure.

Container labeling:
The sponsor was advised of two important changes to avoid medication error and undesirable consequences as listed below. For more details, please see labeling reviews by Zachary Oleszczak of DMEPA, dated November 5 and December 2, 2009

1. The sponsor was advised of changing the color scheme on the container label. The color scheme of gray for the 20 mg tablets and orange for the 40 mg tablets used for the proposed container labels is similar to the color scheme of the currently marketed product. Using a similar color scheme to differentiate the strengths of each product may introduce vulnerability to confusion that could lead to medication errors involving selection of the wrong drug.

2. The sponsor was advised of adding a statement to indicate that two 20 mg tablets should not be used to substitute for one 40 mg tablet (as both the 20 mg and 40 mg tablets contain the same amount of sodium bicarbonate (750 mg) and magnesium hydroxide (343 mg)). **Note:** There were discussions as to whether it is necessary to indicate that one 40mg tablet should not be broken into two pieces to substitute for 20mg tablets. However, since the tablets are not scored, it was decided to be mute on this.

3. DMEPA commented in their review dated December 2, 2009, that the presentation of the established name in the container label is confusing because Sodium Bicarbonate is spilt between two lines of text. DMEPA recommends that the sponsor revise the presentation of the established name on the container labels to ensure **that the words 'Sodium' and 'Bicarbonate' appear on the same line of text.** If necessary the size of the font may be reduced for this purpose, but the same font should be used for the entire established name. In this regard, the sponsor has been advised to revise the container label.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All the primary review disciplines recommended the product for approval. This Reviewer concurs with the recommendation.

13.2 Risk Benefit Assessment

The risk and benefit characteristics for the proposed products appear similar to those of already marketed omeprazole products for the same indications. The product has a favorable risk/benefit profile.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No REMS is recommended with this application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

There are no PMRs for pediatric studies.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The sponsor has requested a full waiver for the pediatric studies for all the indications. We agree with the waiver because of the following reasons:

(1) For the duodenal and gastric ulcer indications, trials would be highly impractical because the number of pediatric patients with the condition is small. Data on the prevalence of gastric or duodenal ulcers in children are scant.[1] Peptic ulcer disease appears to be uncommon in childhood. In large pediatric medical centers with busy gastroenterology practices, only 5 primary ulcers may be diagnosed per year.[2] The annual incidence of primary duodenal ulcers is estimated to be 5 cases per 100,000 children.[2]

References:
1 Oderda,G., Mura S., Valori A., and Brustia R. (2009). "Idiopathic Peptic Ulcers in Children" *Journal of Pediatric Gastroenterology and Nutrition.*48:268-270.
2 Shah, A., Li, B.U., and Carroll M. (2007). "Peptic Ulcer Disease" Retrieved from http://emedicine.medscape.com/article/932308-overview.

(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.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

No PMR studies are recommended.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

No PMC studies are recommended.

13.7 Recommended Comments to Applicant

None.

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

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/s/

SUE CHIH H LEE
12/04/2009