

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-153/ 21-154**

**MEDICAL REVIEW(S)**

Walsh

SEP 21 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-153

Sponsor: AstraZeneca LP (A-Z LP)  
Wayne, PA

Date Submitted: December 3, 1999

Drug: Esomeprazole magnesium (H 199/18; NEXIUM™)

Pharmacological Category: Gastric Acid Antisecretory; Anti-GERD, Anti-Ulcer;  
specific inhibitor of the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system

Formulation/Route of Administration: Delayed-Release Capsules for oral administration

Proposed Indications: a) Healing of Erosive Esophagitis (EE).  
b) Maintenance of Healing of Erosive Esophagitis  
c) Treatment of Symptomatic Gastroesophageal Reflux Disease (s-GERD)

Material Submitted/Reviewed: A total of 359 volumes, including synopsis of application (Item 3, vol. 1, p. 013 through 239), Nonclinical Pharmacology and Toxicology Summary (Item 6), Human Pharmacokinetic and Bioavailability Summary (Item 7), Clinical Summary and Results of Statistical Analyses (Item 8) and Discussion of benefit/Risk Relationship (Item 9).

Reviewer: Hugo E. Gallo-Torres, M.D., Ph.D.  
Medical Team Leader

APPEARS THIS WAY  
ON ORIGINAL

## EXECUTIVE SUMMARY

### I. Recommendation

NEXIUM™ (esomeprazole magnesium; H 199/18), the s-enantiomer of omeprazole and the first proton pump inhibitor (PPI) to be developed as a single isomer, is a substituted benzimidazole derivative that suppresses gastric acid secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system. Like its parent compound (omeprazole) and other PPIs, NEXIUM blocks the final step of gastric secretion and produces dose-related sustained inhibition of both basal and stimulated gastric acid secretion. Like omeprazole and the other approved PPIs, NEXIUM is of benefit in the three gastroesophageal reflux disease (GERD) related indications that require gastric acid inhibition. These indications are: treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic GERD. GERD is a chronic recurring and potentially serious, debilitating condition characterized by symptoms of heartburn and regurgitation. Chronic GERD can lead to morbidity ranging from mild esophageal mucosal inflammation to erosions, ulceration, esophageal stricture and, in some patients, transformation to Barrett's esophagus, a premalignant condition. The data presented by the sponsor in NDA 21-153 demonstrate that NEXIUM a) affords rates of healing which are comparable to omeprazole in the treatment of erosive esophagitis; b) is highly effective in the maintenance of healing of erosive esophagitis and c) provides significantly better rates of symptom resolution within 4 weeks than placebo in patients with symptomatic GERD (s-GERD).

The above-described benefits outweigh the potential risks of this drug. Results of pre-clinical evaluations showed that, at equivalent systemic exposure, H 199/18 is pharmacologically and toxicological (including genotoxicity) similar to omeprazole. Like omeprazole, esomeprazole may be administered with adequate safety to humans at the recommended oral doses and treatment duration. Because NEXIUM™ is the s-enantiomer of omeprazole and omeprazole is a PPI that is perceived as safe, NEXIUM is also considered safe. Omeprazole has been marketed worldwide since 1988 and is presently available in 106 countries for various acid-related gastrointestinal disorders. There have been an estimated \_\_\_\_\_ courses of patient treatments of omeprazole from the time of its introduction into the market through June 30, 1998. This estimate includes all oral formulations of omeprazole. Some patients have received continuous treatment with omeprazole in monitored clinical trials for longer than 13 years [NDA \_\_\_\_\_, 4 August 1999. General Correspondence, omeprazole \_\_\_\_\_], an extensive clinical experience that confirms that omeprazole is – all things considered safe and well-tolerated. Throughout its development and marketing, certain safety issues have been adequately monitored with omeprazole use and comprehensive updates of these topics have been submitted to the Division. It is concluded that based on the clinical experience with esomeprazole, involving over 5,000 patients and subjects, this drug shares the same overall acceptable safety profile of omeprazole.

**The drug is approvable from a clinical perspective. No need for risk management actions is anticipated.**

There are neither recommended Phase 4 trials nor marketing restrictions. Public outreach or information is not needed.

## II. Summary of Clinical Findings

### A. Generalities

- NEXIUM™ (identified in clinical trials as H 199/18 and abbreviated in this review as H) is a gastric acid anti-secretory substituted benzimidazole. This compound belongs to the proton pump inhibitor (PPI) class. NEXIUM™ is the s-enantiomer of omeprazole. PPIs exert their activity through inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme system. This effect abolishes response to all types of gastric acid secretion stimulation, by all gastric messengers (e.g. histamine, gastrin and acetylcholine). NEXIUM™, intended for oral administration, is available as delayed release capsules that bypass the stomach, are absorbed from the intestine and reach the parietal cells via blood, diffusing into the secretory canaliculi. At this site, the (pro)-drug becomes protonated, rearranges to form a sulfenic acid and a sulfenamide and interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane spanning H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme.
- The pharmacological properties of PPIs make them good candidates for treatment of acid-related disorders. This includes GERD, peptic ulcer disease and Zollinger-Ellison syndrome. Indeed, PRILOSEC (omeprazole, abbreviated in this review as O), the parent compound, has been approved for many conditions including short-term treatment of duodenal ulcer, (also in combination with certain antibiotics to eradicate *H. pylori*), short-term treatment of gastric ulcer, treatment of erosive esophagitis (EE), treatment of heartburn and other associated symptoms with GERD (s-GERD), maintenance of healing of EE and the long-term treatment of pathological hypersecretory conditions (e.g. Zollinger-Ellison syndrome).
- The PPIs, especially omeprazole, are perceived as very effective and safe drugs and this is reassuring when assessing the merits of the s-enantiomer of omeprazole. Other approved PPIs are PREVACID (lansoprazole), ACIPHEX (rabeprazole) and recently, PROTONIX (pantoprazole).
- The sponsor submitted the following four groups of trials that evaluated the efficacy and safety of NEXIUM in the treatment of the GERD-related indications for which approval is being sought. All of these studies were well-designed and apparently well-executed, double-blind, randomized, with appropriate: a) controls; b) patient populations; c) consistent inclusion criteria and reasons for exclusion; and d) sufficient sample size for appropriate statistical power. Also consistent were the methods to evaluate efficacy and safety and the timing at which these evaluations were carried out. Esophagogastroduodenoscopy (EGD) was assessed by an appropriate grading scale of esophagitis, the LA Classification.

1. There were four controlled clinical trials in healing of erosive esophagitis:

172 [H40 mg (n= — vs H20 mg (n=656) vs O20 mg (n=650)]

173 [H40 mg (n=576) vs O20 mg (n=572)]

174 [H20 mg (n=588) vs O20 mg (n=588)]

222 [H40 mg (n=1,216) vs O20 mg (n=1,209)]

All four trials were considered pivotal. All four trials used an active comparator, 20 mg of omeprazole (O) once-a-day.

2. There were two controlled clinical trials in maintenance of healing of erosive esophagitis. Both used a negative control (placebo) and were considered pivotal.
- 177 [H40 mg (n=92) vs H20 mg (n=98) vs H10 mg (n=91) vs PL (n=77)]  
 178 [H40 mg (n=82) vs H20 mg (n=82) vs H10 mg (n=77) vs PL (n=77)]
3. There were five controlled clinical trials in the treatment of s-GERD. Of these, the first two used a negative control (placebo) and were considered pivotal. The other three used a positive control (omeprazole 20 mg once-a-day) and were considered supportive.
- 225 [H40 mg (n=123) vs H20 mg (n=121) vs PL (n=124)]  
 226 [H40 mg (n=118) vs H20 mg (n=113) vs PL (n=118)]

**SH-QBE-**

- 0009 [H40 mg (n=425) vs H20 mg (n=423) vs O20 mg (n=434)]  
 -0011 [H40 mg (n=347) vs O20 mg (n=346)]  
 -0021 [H20 mg (n=336) vs O20 mg (n=334)]

4. In addition to the above, there was one noncomparative long-term clinical trial, Study 179, which provided supportive information on the effectiveness of H199/18 in the maintenance of healing of EE. Patients who were determined to be EE healed (LA Classification Grade "Not Present") in Study 173 or Study 174 were eligible to receive open-label H199/18 40 mg qd for 12 months as maintenance treatment. [808 of the 1,157 patients that completed Study 173 and Study 174 as healed were healed were enrolled in Study 179]

**B. Efficacy**

- Efficacy was demonstrated for each of the three indications.
- The recommended claims and daily doses are as follows:
  - 1) Healing of erosive esophagitis  
[20 mg once-a-day for 4 to 8 weeks]
  - 2) Maintenance of healing of erosive esophagitis  
[20 mg once-a-day for at least 6 months]
  - 3) Treatment of symptomatic GERD  
[20 mg once-a-day for 4 weeks]

The indicated population is adult patients with GERD. Efficacy in children has not been assessed but it is not expected to be significantly different from that seen with omeprazole, at the same recommended dose regimen (20 mg once-a-day)

- As summarized below, efficacy in **healing of erosive esophagitis** was shown by demonstrating statistical superiority of H40 to O20 in two trials: 172 and 222. However, in Study 173, H40 was not differentiated from O20. Since, in Study 172, H20 was as efficacious as H40 at both 4 and 8 week evaluations, the reviewer's recommended dose for this indication is 20, \_\_\_\_\_ Moreover, superiority of NEXIUM over omeprazole was not demonstrated because a) in the two studies where H is shown statistically different to O, the dose of H is pharmacodynamically thrice that of the S-isomer in O; b) in spite of this ratio (3:1), H40 was as efficacious as O20 in Study 173;

and c) in Study 174 which used a design that would have shown superiority, if superiority **indeed** exists, the effects of H20 could not be differentiated from O20. These results indicate that for the healing of erosive esophagitis, H20 is as effective as H40. Although the use of H40 is a good scientific tool to demonstrate that - when compared to the recommended dose of O for this indication (20 mg) - esomeprazole is effective in this indication, a superiority claim of NEXIUM over omeprazole is NOT SUPPORTED by either the comparison of H20 vs O20 or the comparison of H40 vs H20.

**Healing of EE**  
**Therapeutic Gain/[p-value]**

Study No.	Time of Evaluation (week)	H40	H40	H20
		vs H20	vs O20	vs O20
172	W4	4.6% [N.S.]	9.7% [<0.001]	N/A
	W8	3.8% [N.S.]	6.2% [<0.001]	N/A
173	W4	N/A	1.9% [N.S.]	N/A
	W8	N/A	1.2% [N.S.]	N/A
174	W4	N/A	N/A	0.8% [N.S.]
	W8	N/A	N/A	2.3% [N.S.]
222	W4	N/A	12% [0.001]	N/A
	W8	N/A	9% [0.001]	N/A

- Efficacy in maintenance of healing of EE was shown in the two placebo-controlled, three-dose-level trials 177 and 178 (see below). In comparison to placebo, all three dose levels of the drug (40, 20 or even 10) are active.

the data show H40 to be superior to H20 in neither of the two trials: in study 177 the therapeutic gain (9.2%) was N.S.; in study 178 the therapeutic gain (0.4%) was also N.S. In addition, because H40 induces significantly higher serum gastrin concentrations

than H20, the reviewer recommends approval of H20 for this indication. For this indication, comparisons to omeprazole are not applicable.

**Maintenance of Healing of EE  
Therapeutic Gain/[p-value]**

Study No.	Time of Evaluation (mo.)	H40 vs PL	H20 vs PL	H10 vs PL	H40 vs H20
177	6	59% [<0.001]	50% [<0.001]	25% [<0.001]	9.2% [N.S.]
178	6	65% [<0.001]	64% [<0.001]	28% [<0.001]	0.4% [N.S.]

- Efficacy in treatment of s-GERD was shown in the two placebo-controlled, two-dose-level trials 225 and 226 (see below). Although both trials showed a lower patient response (complete relief of heartburn) than that seen in EE, this response was well differentiated from placebo. For this indication, as with the previous two, there is no benefit when increasing the H dose from 20 to 40 mg. Thus, the recommended dose of NEXIUM is 20 mg once-a-day. Moreover, claims of superiority to omeprazole are - once again - not supported. Neither H40 (studies -0009 and -0011) nor H20 (Study 021) could be differentiated from O20.

**Treatment of s-GERD  
Therapeutic Gain/[p-value]**

Study No.	Time of Evaluation	H40 vs PL	H20 vs PL	H40 vs H20	H40 vs O20	H20 vs O20
225	W4	20.0% [<0.001]	20.0% [<0.001]	-0.6% [N.S.]	N/A	N/A
226	W4	25.0% [<0.001]	30.0% [<0.001]	-5.0% [N.S.]	N/A	N/A
-0009	W4	N/A	N/A	-3.8% [N.S.]	-1.4% [N.S.]	N/A
0011	W4	N/A	N/A	N/A	2.4% [N.S.]	N/A
021	W4	N/A	N/A	N/A	N/A	2.3% [N.S.]

- As expected of a PPI, the size of treatment effect, especially when compared to placebo, is large and very meaningful clinically. The size of treatment effect in the healing of EE trials is not easily perceived because these are active-active comparator trials. The comparator

(20 mg of omeprazole once-a-day) is very effective in this indication and extremely well differentiated from placebo. This information is described in the package insert for omeprazole. The size of treatment effect in the maintenance of healing of EE is large, a therapeutic gain of at least 50% over placebo in one trial and 64% in the other.

- Finally, the size of treatment effect in s-GERD is good, NEXIUM is reasonably differentiated from placebo in both trials. There is no question that - for this indication - efficacy has been demonstrated. However, NEXIUM (and other PPI, including omeprazole, in other trials) is not very effective in this indication. With 20 mg once-a-day, complete relief of heartburn at Week 4 (Table 54) was seen in only 34% of the patients in one trial and 42% of those in the other. This means that a large proportion of s-GERD patients (66% in one trial and 58% in the other) do not benefit from the administration of this PPI at this daily dose regimen.
- The endpoints studied were reflections of relevant patients benefit and, essentially, attempted to cover all main aspects of GERD. For the healing of EE indication, the effectiveness of the drug was measured by healing of esophageal lesions as verified endoscopically and by symptomatic response [complete relief of heartburn (HB) at the prespecified times (4 and 8 weeks after treatment)]. For the maintenance of healing of EE indication, the effectiveness of the drug was assessed by absence of esophageal lesions upon endoscopy and by lack of appearance of GERD symptoms (HB et al.), both assessed long-term (6 months after randomization to drug or placebo). For the treatment of s-GERD indication, the drug's effectiveness was measured by the clinical endpoint of complete relief of HB at Week 4.
- No comparisons of NEXIUM against H<sub>2</sub>-receptor antagonists have been carried out, but PPIs are usually shown to be superior to H<sub>2</sub>-blockers. NEXIUM is expected to have similar efficacy and safety to the other PPIs approved for GERD-related indications (omeprazole, lansoprazole, rabeprazole and pantoprazole).
- The reviewer reiterates that, \_\_\_\_\_ - this s-enantiomer of omeprazole is of similar efficacy to omeprazole.

### C. Safety

- Safety testing was adequate. All procedures to gather, assemble, analyze and report adverse events and safety-related matters and follow-up when indicated were adequate. The number of patients exposed per indication and the duration of exposure is summarized in Table 55.
- The key safety population consisted of >4,000 patients for the healing of EE indication, 519 + 807 = 1326 patients for the maintenance of healing indication (these patients were treated for 180 days; the exposed number exceeds the ICH number of 300 to 600 to detect an event with a frequency of  $\geq 0.5\%$ ), and 470 + 1530 = 2000 patients for the s-GERD indication.
- Serious side effects were infrequent. For all three indications studied, all serious adverse events (SAEs) were unlikely related to test medication. There is no need for post-marketing monitoring of SAEs.
- The most commonly reported adverse events, per indication, were those related to the G.I. tract plus headache.

AEs

- |                                |  |
|--------------------------------|--|
| - Healing of EE                | Diarrhea, abdominal pain, nausea, flatulence, and headache |
| - Maintenance of Healing of EE | Flatulence, "gastritis"                                    |
| - s-GERD                       | Diarrhea, G.I. symptoms                                    |

In those studies comparing graded dose levels of NEXIUM, there was no dose response. The safety profile seen with H40 and H20 was consistent with that seen with O20.

In the long-term studies of maintenance of healing of EE, the AEs were also predominantly those related to the GI tract.

With the exception of the observed change in serum gastrin concentration, **expected of all PPIs**, there was no indication that treatment with H199/18 for 4 to 8 weeks in the healing of EE, 4 weeks in the treatment of s-GERD and up to 6 months in the maintenance of healing of EE, results in clinically meaningful effects on laboratory values, systolic or diastolic blood pressure, pulse rate, or body weight.

The long-term consequences of hypergastrinemia are still of some concern. This could still be a risk in certain outliers with risk factors. Since there is a dose-response in the average increases in gastrin levels, and H20 mg is effective, \_\_\_\_\_

The changes in ECL cell evaluations, gastritis ratings, chronic inflammation of the gastric mucosa, atrophy, intestinal metaplasia, and atrophic gastritis are very similar to those seen with omeprazole. This database revealed no evidence of dysplasia or neoplasia but only a few cases of adenomatoid hyperplasia [AH]. These EC-L data seem reassuring. However, little is known about long-term (many years of continuous administration) safety of PPIs.

- With NEXIUM, as with other PPIs, the most frequently reported AEs were either GI symptoms or headache. These manifestations are not related to known animal toxicity. The observed ECL cell hyperplasia with omeprazole is seen in all animal species tested. This finding is likely related to the hypergastrinemia induced by this type of drug.
  - Drug-drug interactions are not thought to be a problem with PPIs, NEXIUM included. Listed in the package insert, omeprazole appears to interact with a number of drugs. However, with a few exceptions, identified in the package insert, these drug-drug interactions are not considered to be clinically meaningful.
  - The duration of exposure in the pivotal clinical trials was up to 8 weeks in the healing of EE, 4 weeks in the treatment of s-GERD and up to 6 months in the maintenance of healing of EE. However, GERD is a very chronic condition and patients are treated for years with antisecretory medication.
- [
- The efficacy/safety ratio is acceptable for the requested duration of exposure.
- ]

- NEXIUM should share most of the labeling sections and subsections already incorporated in omeprazole's package insert, including warnings.
- As mentioned above, the safety of NEXIUM relates closely to the other PPIs available for the GERD-related indications.
- There are no unresolved safety issues. No more frequent or serious AEs than those seen with the parent compound, omeprazole are expected. The long-term safety considerations applicable to omeprazole and other approved PPIs apply equally to NEXIUM.

**D. Dosing**

The following NEXIUM doses for the requested indication, are supported by pivotal trials:

- a) 20 mg once-a-day for 4 to 8 weeks for the healing of EE
- b) 20 mg once-a-day for up to 6 months for the maintenance of healing of EE.
- c) 20 mg once-a-day for 4 weeks for the treatment of s-GERD.

**E. Special Populations**

NEXIUM demonstrated efficacy for both male and female patients. Races, other than Caucasian and the elderly, were not appropriately represented in the clinical trials.

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## TABLE OF CONTENTS

	Page
Executive Summary	2
<b>I. BACKGROUND</b>	<b>17</b>
A. Gastroesophageal Reflux Disease (GERD)	17
B. Esomeprazole magnesium (ESOME Mg)	21
1. Introduction	21
2. Brief Summary of Nonclinical Pharmacology	22
3. Brief Summary of Toxicology and Drug Metabolism	23
4. Summary of Human PKs and Bioavailability	24
5. Summary of Human Pharmacodynamics	27
6. Foreign Marketing History	29
<b>II. REQUESTED LABELING FOR THE THREE INDICATIONS SOUGHT</b>	<b>29</b>
<b>III, RATIONALE FOR TESTING EFFICACY AND SAFETY OF THE ESOME Mg AT THE SPECIFIED ONCE-A-DAY DOSES FOR EACH OF THE THREE INDICATIONS SOUGHT</b>	<b>32</b>
<b>IV. CRITICAL CLINICAL TRIALS IN NDA 21-153</b>	<b>34</b>
<b>V. REVIEW OF CLINICAL TRIALS FOR THE INDICATION SHORT-TERM HEALING OF EROSIIVE ESOPHAGITIS</b>	<b>38</b>
A. Study 172	38
1. Primary Objective	38
2. Secondary Objectives	38
3. Study Population	38
4. Overall Study Design and Schedule of Evaluations	40
5. Clinical Supplies/Randomization/Selection of Timing of Dose for Each Patient/Blinding	41
6. Prior and Concomitant Therapy: Compliance	42
7. Evaluation Criteria	43
a) Efficacy	43
b) Safety, Dictionaries and Coding Terminology	43
8. Data Quality Assurance	43
9. Statistical Methodology (As Prespecified in the Protocol)	43
a) Determination of Sample Size	43
b) Details of Statistical and Analytical Procedures	43
10. Results	45
a) Disposition of Patients/Per Protocol Deviations	45
b) Data Showing Comparability of Treatment Groups at Baseline	47
c) Compliance	48
d) Proportion of Patients Healing After 4 and 8 Weeks	48

	<u>Page</u>
e) Erosive Esophagitis Healing Rates by Baseline Severity	51
f) Proportion of Patients Who Exhibited Complete Resolution of Investigator-Recorded Symptoms of GERD after 4 Weeks	51
g) Assessment of Healing of EE by Subgroups	52
h) Results of Safety Evaluations	53
i) Extent of Exposure	53
ii) Deaths, Other Serious and Potentially Serious AEs	54
iii) AEs Leading to Discontinuation	54
iv) Adverse Events	56
v) Changes in Laboratory Parameters/Serum Gastrin	58
vi) Other	59
11. Discussion and Overall Conclusions (Sponsor)	59
12. Reviewers Additional Comments	59
<b>B. Study 173</b>	<b>61</b>
1. Primary Objectives	61
2. Secondary Objectives	61
3. Study Population	61
4. Overall Study Design and Schedule of Evaluations	61
5. Clinical Supplies/Randomization/Selection of Timing of Dose for Each Patient/Blinding	62
6. Prior and Concomitant Therapy: Compliance	62
7. Evaluation Criteria	62
8. Data Quality Assurance	62
9. Statistical Methodology	63
a) Determination of Sample Size	63
b) Details of Statistical and Analytical Procedures	63
10. Results	63
a) Disposition of Patients/Per Protocol Deviations	63
b) Data Showing Comparability of Treatment Groups at Baseline	64
c) Compliance	66
d) Proportion of Patients Healing After 4 and 8 Weeks	66
e) EE Healing Rates by Baseline Severity	67
f) Results of Safety Evaluations	68
11. Discussion and Overall Conclusions (Sponsor)	68
12. Reviewer's Additional Comments	69
<b>C. Study 222</b>	<b>69</b>
1. Primary Objectives	70
2. Secondary Objectives	70
3. Study Population	70
4. Overall Design and Schedule of Evaluations	70
5. Clinical Supplies/Randomization/Selection of Timing of Dose for Each Patient/Blinding	71

	<u>Page</u>
6. Prior and Concomitant Therapy: Compliance	71
7. Evaluation Criteria	71
8. Data Quality Assurance	71
9. Statistical Methodology	72
10. Results	76
a) Disposition of Patients/Per Protocol Deviations	76
b) Data Showing Comparability of Treatment Groups at Baseline	78
c) Compliance	78
d) Proportion of Patients Healing After 4 and 8 Weeks	80
e) EE Healing by Baseline Severity	82
f) Proportion of Patients Who Exhibited Complete Resolution of Investigator-Recorded Symptoms of GERD After 4 Weeks	82
g) Assessment of Healing of EE Subgroups	83
h) Results of Safety Evaluations	83
i) Extent of Exposure	83
ii) Deaths, Other Serious or Potentially Serious AEs	83
iii) AEs Leading to Discontinuation	84
iv) Adverse Events	86
v) Changes in Laboratory Parameters/Serum Gastrin	86
vi) Other	88
11. Discussion and Overall Conclusions (Sponsor)	89
12. Reviewer's Additional Comments	89
VI. REVIEW OF CLINICAL TRIALS SUBMITTED IN SUPPORT OF THE INDICATION MAINTENANCE OF HEALING OF EROSIIVE ESOPHAGITIS	 91
A. Study 177	91
1. Primary Objective	91
2. Secondary Objective	91
3. Study Population	91
4. Overall Study Design and Schedule of Evaluations	93
5. Clinical Supplies/Randomization/Selection of timing of Dose for Each Patient/Blinding	94
6. Criteria for Evaluation of Efficacy	94
7. Criteria for Evaluation of Safety	95
8. Statistical Methodology	96
a) Determination of Sample Size	96
b) Details of Statistical and Analytical Procedures	96
9. Other Aspects of the Study	97
10. Results	97
a) Disposition of Randomized Patients/Protocol Deviations/ Exclusions from the PP Population and Summary of Patient Disposition and EGD Evaluability	97
b) Data Showing Comparability of Treatment Groups at Baseline	99
c) Compliance	99

	<u>Page</u>
d) Evaluation of Maintenance of Healing	99
e) Summary Results of Secondary Evaluation Parameters	102
f) Results of Safety Evaluations	102
i) Extent of Exposure	102
ii) Deaths, Other Serious and Potentially Serious AEs	104
iii) AEs Leading to Discontinuation	104
iv) Adverse Events	107
v) Changes in Laboratory Parameters/Serum Gastrin	109
vi) Other	109
11. Sponsor's Discussion and Overall Conclusion	110
12. Reviewer's Additional Comments	111
<b>B. Study 178</b>	<b>112</b>
1. through 4. Primary and Secondary Objectives, Study Population, Overall Design and Schedule of Evaluations	113
5. Clinical Supplies, Randomization/Selection of Timing of Dose for Each Patient/Blinding	113
6. and 7. Criteria for Evaluation of Efficacy and Safety	113
8. Statistical Methodology	113
9. Other Aspects of the Study	113
10. Results	113
a) Disposition of Randomized Patients/Protocol Deviations/ Exclusions From the PP Population and Summary of Patient Disposition and EGD Evaluability	113
b) Data Showing Comparability of Treatment Groups at Baseline	114
c) Compliance	114
d) Evaluation of Maintenance of Healing	115
i) Mean Time to Recurrence	118
ii) Examination of Subgroups	118
e) Summary Results of Secondary Efficacy Parameters	119
f) Results of Safety Evaluations	120
i) Extent of Exposure	120
ii) Deaths, Other Serious and Potentially Serious AEs	121
iii) AEs Leading to Discontinuation	122
iv) Adverse Events	123
v) Changes in Laboratory Parameters/Serum Gastrin	124
vi) Other	125
11. Sponsor's Discussion and Overall Conclusion	126
12. Reviewer's Additional Comments	127
<b>VII. REVIEW OF CLINICAL TRIALS FOR THE INDICATION TREATMENT OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (s-GERD)</b>	<b>128</b>
<b>A. Study No. 225</b>	<b>128</b>
1. Primary Objective	129

	<u>Page</u>
2. Secondary Objectives	129
3. Study Population	130
4. Overall Study Design and Schedule of Evaluation	131
5. Clinical Supplies/Randomization/Selection of Doses and Timing of Dosing/Blinding	132
6. Prior and Concomitant Therapy/Compliance	133
7. Evaluation Criteria	133
a) Efficacy	133
b) Safety, Dictionaries and Coding Safety Terminology	133
8. Data Quality Assurance	134
9. Statistical Methodology	134
a) Determination of Sample Size	134
b) Details of Statistical and Analytical Procedure	134
10. Results	135
a) Disposition of Patients/Protocol Deviations	135
b) Data Showing Comparability of Treatment Groups at Baseline	135
c) Compliance	135
d) Proportion of Patients With Complete Resolution of HB at Final Visit	137
e) Proportion of Patients With Complete Resolution of HB at 1, 2 and 4 Weeks	138
f) Other Secondary Efficacy Parameters	139
g) Analysis of the Primary Efficacy Endpoint by Subgroups	140
h) Results of Safety Evaluations	142
i) Extent of Exposure	142
ii) Deaths and Other SAEs	142
iii) AEs Leading to Discontinuation	142
iv) adverse Events	143
v) Changes in Laboratory Parameters/Serum Gastrin	143
11. Sponsor's Discussion and Overall Conclusions	144
12. Reviewer's Additional Comments	144
 B. Study No. 226	 145
1. Primary Objective	145
2. Secondary Objectives	145
3. Study Population	145
4. Overall Study Design and Schedule of Evaluations	145
5. Clinical Supplies/Randomization/Selection of Doses and Timing of Dosing/Blinding	146
6. Prior and Concomitant Therapy/Compliance	146
7. Evaluation Criteria	146
a) Efficacy	146
b) Safety, Dictionaries and Coding Safety Terminology	146
8. Data Quality Assurance	146

	<u>Page</u>
9. Statistical Methodology (as specified in the Protocol)	146
10. Results	147
a) Disposition of Patients/Protocol Deviations	147
b) Data Showing Comparability of Treatment Group at Baseline	149
c) Compliance	150
d) Proportion of Patients with Complete Resolution of HB at Final Visit	150
e) Proportion of Patients With Complete Resolution of HB at 1, 2, and 4 Weeks	151
f) Other Secondary Parameters of Efficacy	152
g) Analysis of Primary Efficacy Endpoint by Subgroups	153
h) Results of Safety Evaluations	154
i) Extent of Exposure	154
ii) Deaths and Other SAEs	155
iii) AEs Leading to Discontinuation	155
iv) Adverse Events	156
v) Changes in Laboratory Parameters/Serum Gastrin	156
11. Sponsor's Discussion and Overall Conclusions	157
12. Reviewer's Additional Comments	157
VIII. INTEGRATED SUMMARY OF EFFICACY	158
A. Generalities/Questions to be Addressed	158
B. Healing of Erosive Esophagitis	161
C. Maintenance of Healing of Erosive Esophagitis	161
D. Treatment of s-GERD	162
E. Overall Conclusions on Efficacy	162
IX. INTEGRATED SUMMARY OF SAFETY	163
A. Generalities	163
B. Safety Data From Healing of EE Studies	164
C. Safety Data From s-GERD Studies	165

	<u>Page</u>
D. Safety Data From Maintenance of Healing of EE Studies	165
E. Uncontrolled, Long-Term Safety (Study 179)	167
1) Highlights of Results of Safety Evaluations	167
2) Gastritis Ratings and ECL Cell Evaluations	168
i) ECL cell Ratings	168
ii) Chronic Inflammation	169
iii) Atrophy	169
iv) Summary of Gastritis Evaluation	170
v) Atrophic Gastritis	170
F. Summary Findings on Changes of Serum Gastrin Concentration Across Clinical Trials in NDA 21-153	170
X. SUMMARY OF BENEFITS vs RISKS	171
XI. FINANCIAL DISCLOSURE	172
XII. RECOMMENDATIONS FOR REGULATORY ACTION	173

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## I. BACKGROUND

### A. Gastroesophageal Reflux Disease (GERD)

In this section, a brief description of the clinical condition(s) to be treated is given, with emphasis on the three indications being sought.

GERD is a clinical disorder caused by the retrograde flow of gastric and duodenal contents across an incompetent gastroesophageal junction into the esophagus. Although GERD is primarily a motility disorder of the upper gastrointestinal tract, understanding the pathogenesis of GERD necessitates understanding of the normal physiologic barriers to reflux. Organs involved include the lower esophageal sphincter (LES), the body of the esophagus, the stomach, and perhaps the antropyloroduodenal antireflux mechanism.

- As recently reviewed by Robert S. Fisher<sup>1</sup>, the major barrier to GER is the LES<sup>1</sup>. Three categories of LES abnormality have been described in patients with GERD<sup>2</sup>. First, resting (basal) LES may be reduced, especially in patients with severe esophagitis and complications of GERD such as stricture and Barrett's esophagus.<sup>3</sup> LES hypotension may be aggravated by a number of external factors.<sup>4</sup> Second, abnormal adaptive LES responses to increased intra-abdominal pressure, to meal ingestion, and to gastric distention have been reported in patients with GERD.<sup>5</sup> Third and perhaps most important, spontaneous, transient (inappropriate) LES relaxations that are not clearly associated with swallowing, esophageal distention, or esophageal peristalsis have been described in patients with GERD.<sup>6</sup> Reflux of acidic gastric contents into the esophagus has been demonstrated during these spontaneous relaxations of the LES. This phenomenon may be present in up to 60% of patients with GERD, especially those with a normal endoscopic examination.<sup>7</sup>

<sup>1</sup> [The Therapy of Digestive Disorders, M. Michael Wolfe, editor. Chapter 1: Treatment of Gastroesophageal Reflux Disease. W.B. Saunders Co., Philadelphia, 1999, pp3-16]

<sup>2</sup> [W.J. Dodds et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *NEJM* 307:1547-1552 (1982)]

<sup>3</sup> [S. Cohen, L.D. Harris. Does hiatus hernia affect competence of the esophageal sphincter? *NEJM* 284:1053-1056 (1971)]

<sup>4</sup> This includes foods such as fat, chocolate, and carminatives; medications such as oral contraceptives, narcotic analgesics, anticholinergics, and calcium channel blockers; smoking and pregnancy [D.O. Castell. *Ann. Intern. Med.* 104:112-114 (1996)].

<sup>5</sup> [J. Dent et al. Mechanisms of lower esophageal sphincter incompetence in patients with symptomatic gastroesophageal reflux. *Gut* 29:1020-1028 (1988)]

<sup>6</sup> [R.K. Mittal et al. Characteristics and frequency of transient relaxations of the lower esophageal sphincter in patients with reflux esophagitis. *Gastroenterology* 95:593-599 (1988); Transient lower esophageal sphincter relaxation. *Gastroenterology* 109:601-610 (1995)]

<sup>7</sup> [J. Dent et al., locus cited (1988)]

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- The importance of hiatal hernia in GERD is controversial.<sup>8</sup>
- Esophageal peristalsis, gravity, and the availability of saliva are major determinants of esophageal clearance.<sup>9</sup>
- When patients are recumbent (during sleep), gravity is lost as a propulsive clearance force. In addition, the contact time between the esophageal mucosa and the gastric refluxate may be prolonged during sleep because the frequency of swallowing, the stimulus for primary peristalsis, decreases from approximately 60 to 90 times per hour during awake hours to 4 to 6 times per hour during sleep.<sup>10</sup> Moreover, during sleep and especially in patients with GERD, salivary volume and bicarbonate may be reduced.<sup>11</sup>
- Gastroparesis has been reported in >40% of patients with reflux esophagitis.<sup>12</sup> Retained gastric contents might produce gastric distention, which could result in diminished LES pressure and perhaps induce "inappropriate" LES relaxation. A few studies have reported excessive regurgitation of bile salts into the stomach in patients with GERD, especially when benign distal esophageal strictures and Barrett's esophagus are present. Such excessive bile salt regurgitation would suggest that antropyloroduodenal coordination may be disrupted.
- Nonmotility factors are noted [R.S. Fisher (locus cited) (1999)]. The gastroesophageal refluxate in patients with GERD contains acid, pepsin, digestive products, and occasionally bile salts. Acid hypersecretion has not been established for the majority of patients with GERD [B.I. Hirschowitz *Gastroenterology* 101:1149-1158 (1991)]. Patients with gastrinomas are more susceptible to the development of severe refractory esophagitis [L.S. Miller et al. *Gastroenterology* 98:341-348 (1990)]. Basal hypersecretion of acid [basal acid output (BAO), >10 mEq/h] even when a gastrinoma is not present, may be a contributing factor to refractory symptoms and/or esophagitis. Collen and associates [*Gastroenterology* 98:654-661 (1990)] have demonstrated in some patients that symptoms abate and esophagitis heals only when basal acid output is reduced below 1.0 mEq/h. These findings

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<sup>8</sup> Hiatal hernias are associated with a decreased intra-abdominal length of the LES, dysfunction of the crural diaphragmatic muscle fibers, and perhaps, abnormal function of the phrenoesophageal ligaments. Several investigators have confirmed that the crural diaphragm may be an important component of the antireflux barrier of the gastroesophageal junction [S. Sloan et al. *Ann. Intern. Med.* 117:977-982 (1992); W.A. Klein et al. *Gastroenterology* 105:362-369 (1993)]

<sup>9</sup> Abnormalities of esophageal peristalsis have been described not only in primary motor disorders of the esophagus associated with GERD, such as scleroderma, but also in patients with uncomplicated GERD. Decreased amplitudes and incoordination between distal esophageal contractions have been reported [K.M. Cunningham et al. *Gut* 32:1436-1440 (1991); R. Timmer et al. *Gut* 34:317-320 (1993)]

<sup>10</sup> [W.C. Orr et al. Effect of sleep on swallowing, esophageal peristalsis and acid clearance. *Gastroenterology* 86:814-819 (1984)]

<sup>11</sup> [J.F. Helm et al. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. *NEJM* 310:284-288 (1984)]

<sup>12</sup> [S.S. Shay et al. Gastric emptying of solid food in patients with gastroesophageal reflux. *Gastroenterology* 92:459-465 (1987)]

may be of practical utility at least in the treatment of certain patients. The evidence supporting a role for bile salts and/or pancreatic enzymes in the development of uncomplicated GERD remains controversial.

- An additional potentially important factor in the pathogenesis of GERD is the intrinsic tissue resistance of stratified squamous epithelium. It has been demonstrated that esophageal mucosa secretes bicarbonate, which may act as a local defense mechanism [C.M. Brown et al. *Gut* 34:872-880 (1993); S. Singh et al. *Gut* 34:309-316 (1993)]. As mentioned above, another and perhaps more important source of esophageal bicarbonate is saliva. Both decreased salivary volume and decreased salivary bicarbonate have been reported in patients with GERD. The role of epidermal growth factor and esophageal mucus in GERD is a subject of current interest.
- Symptoms of GERD could be: a) esophageal (heartburn, regurgitation, dysphagia, water brash and chest pain); b) extraesophageal<sup>13</sup>; and c) augmented sensitivity. Some patients, even with erosive esophagitis or Barrett's esophagus, are asymptomatic or nearly asymptomatic.
- As noted in Fisher's recent review [(locus cited) (1999)], GERD symptoms may relate to the direct irritant effects of the gastric refluxate on esophageal mucosa or may result from intraesophageal or extraesophageal complications of GERD. **Heartburn (pyrosis)** the *sine qua non* of GERD, refers to a retrosternal burning discomfort that radiates cephalad from the xyphoid toward the neck. It may be exacerbated by eating certain foods, bending, or lying down, and it may be relieved, at least transiently, by ingestion of antacids. Heartburn may correlate with excessive esophageal acid exposure and a drop in esophageal pH below 4.0.<sup>14</sup> Rosen and Pope<sup>15</sup> reported significant heartburn in some patients despite normal acid exposure recorded on prolonged esophageal pH monitoring. Nevertheless, these patients respond to acid suppression therapy, thus suggesting that they may have **augmented esophageal sensitivity** to normal acid exposure.<sup>16</sup> Regurgitation, another symptom classically associated with GERD, is defined as the passive movement of chyme across the gastroesophageal junction into the esophagus, often extending into the mouth and resulting in a bitter or acidic taste. Regurgitation may be aggravated by recumbency during sleep or

<sup>13</sup> Pulmonary wheezing, coughing, sleep apnea, Otolaryngologic: hoarseness, sore throat, globus. Dental: gingivitis, bad breath, enamel pits. Gastric: early satiety, nausea, bloating, pain.

<sup>14</sup> [S. Mattioli et al. Reliability of 24-hour home esophageal pH monitoring in diagnosis of gastroesophageal reflux. *Dig Dis Sci* 14:71-78 (1989)]

[F. Johnson et al. Symptoms and endoscopic findings in the diagnosis of gastro-esophageal reflux disease. *Scand. J Gastroenterol* 22:714-718 (1987)]

[A.G. Klauser et al. Symptoms in gastro-oesophageal reflux disease. *Lancet* 335:205-208 (1990)]

[D.J. Ott et al. Heartburn correlated to 24-hour pH monitoring and radiographic examination of the esophagus. *Am J Gastroenterol* 92:1827-1830 (1997)]

<sup>15</sup> [S.N. Rosen and C.E. Pope, Extended esophageal pH monitoring. An analysis of the literature and assessment of its role in the diagnosis and management of gastroesophageal reflux. *J Clin Gastroenterol* 11:260-270 (1989)]

<sup>16</sup> R.G.P. Watson et al. Double-blind, cross-over, placebo-controlled study of omeprazole in the treatment of patients with reflux symptoms and physiologic levels of acid reflux - The "sensitive esophagus." *Gut* 40:587-590 (1997)]

by increased intra-abdominal pressure during straining at defecation, exercise, or bending over. In some cases, recumbent regurgitation may be associated with nocturnal aspiration causing choking, coughing or wheezing.

- Treatment of GERD is based on four physiologic, but not necessarily sequential principles: improvement in gastroesophageal junction antireflux function, augmentation of the esophageal clearance mechanism, decrease in volume and potency of the gastroesophageal refluxate, and protection of the esophageal mucosa from acid-inducing injury.
- Most gastroenterologists use either a "step-up" or a "step-down" regimen in treating patients with GERD. The time-honored step-up regimen begins with behavior modification and over-the-counter (OTC) acid neutralization or suppression and works its way up to robust acid suppression with proton pump inhibitors (PPIs). The step-down regimen begins with robust acid suppression and works its way down to H<sub>2</sub> receptor antagonists, promotility compounds, and even behavior modification. It is important to note that little evidence has been published to date that patients with GERD can be stepped down from PPIs.

## INDICATIONS

Clinically, two main forms of GERD are recognized: erosive esophagitis, where symptoms of reflux are accompanied by esophageal damage (i.e. erosions, ulcer), and symptomatic GERD (s-GERD), where symptoms of reflux (mainly diurnal and nocturnal heartburn) are not associated with endoscopically proven esophageal damage. The differentiation between these two forms of GERD is clinically important because erosive esophagitis (but not symptomatic GERD) may give rise to serious complications such as esophageal narrowing and stricture, esophageal ulcer and hemorrhage, pulmonary aspiration, or Barrett's esophagus (a premalignant condition). It is important to state that the amount of gastric acid antiseptics (H<sub>2</sub>-blockers) to treat erosive disease is usually higher (and in the case of H<sub>2</sub>-blockers must be administered in divided doses) than that needed to treat symptomatic GERD. However, in the U.S., the dose for omeprazole, the PPI used as comparator in clinical trials in the present NDA, is the same (20 mg once-a-day) for both indications. Many patients with GERD require long-term (L-T) maintenance (the third indication). The efficacy of an agent for L-T maintenance may well be affected by the treatment used initially (during the acute phase) to achieve clinical remission. One important clinical principle is that PPIs and high-dose H<sub>2</sub>-receptor antagonists should be reserved for patients who do not respond to either H<sub>2</sub>-receptor antagonists (H<sub>2</sub>-RAs; at usual doses) or promotility agents alone or for those who have complicated GERD (grade 3 or 4) endoscopically proven esophagitis, a benign esophageal stricture, or Barrett's esophagus.

- Finally, it is worth noting that one sensitive test for the presence of acid reflux consists of monitoring esophageal pH with a luminal pH probe for periods of up to 24h. Concerns have been expressed about the use of a single probe of intragastric pH. Poor correlation exists between single-point electrode recording of pH and the more integrated values obtained from aspirated gastric juice samples on which the pH is measured *in vitro*

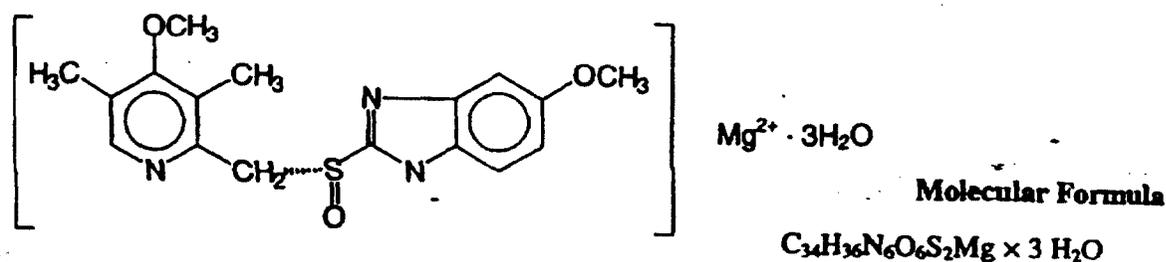
immediately after aspiration. Raised pH cannot be accepted as a surrogate for clinical benefit, especially in functional disorders of the upper GI tract. In addition, although 24-h esophageal pH monitoring may show that reflux indeed exists, it does not necessarily follow that reflux is responsible for the patient's symptoms. Furthermore, symptoms due to acid reflux do not always correlate with the extent of damage to the esophageal mucosa. Endoscopy with suction biopsy is the most sensitive test for reflux-induced mucosal damage, but in clinical trials, biopsy is usually omitted.

## **B. Esomeprazole Magnesium (ESOME Mg)**

### **1. Introduction**

ESOME Mg is a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of the action of the enzyme  $H^+/K^+$ -ATPase. ESOME Mg is the **S-enantiomer** of omeprazole (OME). The ultimate mediator of acid secretion is the  $H^+/K^+$ -ATPase ("proton pump") of the apical membrane of the parietal cell. This proton pump exchanges luminal potassium for cellular hydrogen ions [E.E. Fellenires et al. Nature 290:159-161 (1981)]. Inhibition of the proton pump by ESOME Mg [and approved PPIs, i.e. omeprazole (OME-), lansoprazole (LANZO-), rabeprazole (RABE-) and pantoprazole (PANTO)] abolishes response to all types of acid secretion stimulation, by all gastric messengers (e.g. histamine, gastrin, and acetylcholine). When stimulated to secrete acid, the gastric parietal cell undergoes morphologic alteration with formations of secretory canaliculi. **All** PPIs contain a sulfinyl group in a bridge between substituted benzimidazole and pyridine rings. At neutral pH, all PPIs are chemically stable, lipid-soluble, weak bases that are devoid of inhibitory activity. These neutral weak bases reach parietal cells from the blood and diffuse into the secretory canaliculi, where the drugs become protonated and thereby trapped. The protonated agent rearranges to form a **sulfenic acid and a sulfenamide**. The latter interacts covalently with sulfhydryl groups at critical sites in the extracellular (luminal) domain of the membrane-spanning  $H^+/K^+$ -ATPase. Full inhibition occurs with two molecules of inhibitor bound per molecule of enzyme. The PPIs must thus be considered as **prodrugs** that need to be activated to be effective. The specificity of the effects of PPIs derive from the selective distribution of  $H^+/K^+$ -ATPase, from the requirement for acidic conditions to catalyze generation of the reactive inhibitor, and from trapping of the protonated drug and the cationic sulfenamide within the acidic canaliculi and adjacent to the target enzyme. Administration of omeprazole or ESOME Mg results in permanent inhibition of enzyme activity *in vivo*; secretion of acid resumes only after insertion of new molecules of  $H^+/K^+$ -ATPase into the luminal membrane.

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**Di-(S)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]sulfinyl]-1 H-benzimidazole magnesium trihydrate**

**Fig. 1. - Clinical Structure of ESOME Mg**

The molecule contains one asymmetrically substituted sulfoxide moiety, which makes the molecule chiral. In ESOME Mg the sulfur has the (S)-configuration.

**2. Brief Summary of Nonclinical Pharmacology**

Since, at this point in time a Pharmacology/Toxicology Review is not available, the following information was summarized from the sponsor's Application Summary (vol. 4 of 359, Item 3) (only major findings from the sponsor's program are highlighted). [Note, H199/18 = ESOME Mg = H].

- The anti-secretory potencies of H 199/18 and racemic OME were **equivalent** in rats.
- In rats, exposure to H 199/18 increased more than proportionally to the increase in dose, the C<sub>max</sub> and AUC values were similar after treatment with equivalent doses of H 199/18 or OME and higher plasma concentrations of both compounds were noted in females compared to males. Values seen in pregnant rats were of the same order of magnitude as those noted in non-pregnant females.
- In dogs, exposure after oral administration of the same dose of the two compounds was **equivalent**. There were no significant differences between single and repeated administration or between Ms and Fs, and the exposure to H 199/18 increased in approximate proportion to dose. The exposure in relation to the given dose was considerably higher in the dog than in the rat, but the actual exposures at the highest dose levels used in the repeated dose toxicology studies were similar.
- There were **no differences in excretion routes and recovery** between H 199/18 and OME in dogs. Both compounds were metabolized via the same biotransformation routes to the same primary metabolites.

- Correlation between the given dose and the  $C_{max}$  and AUC values was difficult in the pregnant rabbit, as a pronounced inter-individual variation was noted. However, significantly higher values were seen after repeated-administration compared to single-administration of H 199/18, and no significant differences were found between equivalent doses of H 199/18 and OME. Exposure in the rabbits was relatively low compared to that in rats.
- H 199/18 was stable against racemization and inversion *in vivo* in both rats and dogs.

### 3. Brief Summary of Toxicology and Drug Metabolism

The sponsor states:

- The acute toxicity of H 199/18 was low after both oral and I.V. administration to rats and was equivalent to that of OME.
- Repeated oral treatment of rats at dose levels of 200, 400 or 800  $\mu\text{mol/Kg}$  (69, 140 or 280 mg/Kg) H 199/18 or 400  $\mu\text{mol/Kg}$  (140 mg/Kg) OME resulted in some slight hematological changes (decreases in the red cell variables).

These changes indicate a microcytic anemia, possibly due to an iron deficiency. They were, however, only slight, were noted at high dose levels only and have previously been observed after OME treatment. Similar slight changes were seen in pregnant rabbits, but no such changes were noted in dogs.

- In both rats and dogs, histopathological changes in the stomach (a dose dependent chief cell eosinophilia or atrophy, mucosal hyperplasia or fibrosis and/or focal necrosis of the gastric glands), accompanied by a dose-dependent increase in stomach weight and **serum gastrin levels**, were noted at the higher dose levels of both compounds. These changes were **expected**, are consistent with previous observations following treatment with high doses of OME and are thought to be a result of gastrin stimulation and/or inhibition of gastric acid secretion.
- Slight maternal toxicity (reduced body weight gain and food consumption) was noted in pregnant rats treated orally with 200 or 800  $\mu\text{mol/Kg}$  (69 or 280 mg/Kg) H 199/18 or 400  $\mu\text{mol/Kg}$  (140 mg/Kg) OME. However, no adverse effects could be detected on embryo-fetal survival or development. According to the sponsor, the systemic exposure to H 199/18 in these animals was substantially higher than that seen in the clinical situation, indicating an adequate margin of safety.
- The treatment of pregnant rabbits with oral doses of up to 250  $\mu\text{mol/Kg}$  (86 mg/Kg) H 199/18 or 80  $\mu\text{mol/Kg}$  (38 mg/Kg) OME did not indicate any potential for disturbance of embryo-fetal development. Maternal toxicity (a dose dependent absolute loss in body

weight or a reduced body weight gain, accompanied by reduced food and water consumption and a decreased fecal output) was noted at 80 and 250  $\mu\text{mol/Kg}$  (28 and 86 mg/Kg) H 199/18 and 80  $\mu\text{mol/Kg}$  (28 mg/Kg) OME. Some small litter effects (slightly reduced mean fetal and litter weights and a small increase in the incidence of minor skeletal defects) were observed at 250  $\mu\text{mol/Kg}$  H 199/18, but were considered to be related to this maternal toxicity rather than to be a direct effect on embryo-fetal development. Although exposure was relatively low in many animals, the highest dose level could not be increased in the main study due to a severe, dose-related maternal toxicity at doses higher than 250  $\mu\text{mol/Kg}$ .

- H 199/18 was not mutagenic in an Ames test *in vitro*. A chromosome aberration test in peripheral human lymphocytes showed that H 199/18 is **clastogenic** under certain *in vitro* test conditions. Two *in vivo* cytogenetic tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rats) in the presence of high systemic exposure to H 199/18 (in the same range as the lowest concentration that induced chromosome aberrations *in vitro*) showed that H 199/18 was **not clastogenic under *in vivo* conditions**. It is to be noted that exposure levels encountered in man are well below those at which clastogenic effects occurred *in vitro*. But in reality, it is not yet established if these comparisons are pertinent.

Based on the results in these tests the sponsor concluded that H 199/18 does not represent a genotoxic risk to man. Again, the final court of inquiry should be clinical experience for a number of years of continuous administration of PPIs.

- The effects after repeated oral administration to rats or dogs indicated that H 199/18 has a low systemic toxicity. In addition, all the effects noted have also been seen after treatment with OME, either in the reference groups given OME in the studies summarized here or in previous toxicology studies on OME itself. The sponsor speculates that the few quantitative differences that were noted could be attributed to a higher exposure to the drug at the highest given doses of H 199/18, compared to the given doses of OME.

**NOTE:** The reviewer agrees with the sponsor's conclusion that the documentation presented in NDA 21-153 shows that the enantiomer H 199/18 has a similar pharmacological and toxicological profile to that of racemic OME. Therefore, all the nonclinical studies previously performed on OME may be used to evaluate the nonclinical effects and support the clinical use of H 199/18. As previously mentioned, distant safety issues are still unresolved.

In the summary volume, no detailed data on the metabolism of ESOME Mg in animals was presented.

#### **4. Summary of Human PKs and Bioavailability**

Reproduced below are the sponsor's conclusions.

H 199/18 and H 199/19, or S-OME and R-OME, respectively, are the two OME enantiomers. H 199/18 was developed as a drug to be used for treatment of acid-related diseases. This summary on PKs and bioavailability of H 199/18 is based on data obtained from three preclinical *in vitro* studies on human material, such as human liver microsomes, and from 26 clinical pharmacology studies with H 199/18 administered *in vivo*. Six additional studies were conducted with the \_\_\_\_\_ tablet formulation and are used only in the pooled analysis on potential gender differences in PKs. Ca. 600 healthy subjects, of which 1/3 was of F gender, and 65 subjects from different patient populations (GERD patients warfarin-treated subjects, and phenytoin-treated subjects) were recruited for these investigations. The majority of subjects were of Caucasian origin. I.V. administration of H 199/18 was used in two studies while the other studies used only oral dosing with either solution or capsule formulations.

- *In vitro* experiments showed that for both enantiomers, H 199/18 and H 199/19, the formation of the sulphone is via CYP3A4, while that of the hydroxy- and 5-*O*-desmethyl-metabolites is via CYP2C19, and the affinity to CYP2C19 is ca. one order of magnitude higher than to CYP3A4.
- The rate of formation of the hydroxy-metabolite from H 199/18 was lower and that of the two other metabolites was higher compared to H 199/19, thus demonstrating a difference in metabolic profile between the two enantiomers. The sum of the intrinsic clearance values of all three metabolites was three times lower for H 199/18 than for H 199/19, indicating that H 199/18 would be cleared more slowly than H 199/19 *in vivo*. In addition, *in vitro* studies demonstrated that H 199/18 was 97% bound to plasma proteins.

The following types of studies were carried out: PKs after single and repeated dosing, interactions with other drugs and food, bioavailability and bioequivalence evaluations. Brief summary of the conclusions reached by the sponsor follows.

### Pharmacokinetics

- H 199/18 was optically (enantiomerically) stable and the degree of inversion in man is negligible.
- H 199/18 was 97% bound to plasma proteins.
- *In vitro* experiments demonstrated that both H 199/18 and H 199/19 are metabolized by CYP2C19 (hydroxy- and 5-*O*-desmethyl- metabolites) and CYP3A4 (sulphone). The affinity to CYP2C19 was approximately one order of magnitude higher than to CYP3A4. However, there was a difference in metabolic profile between the two enantiomers. This difference resulted in a three times lower intrinsic clearance for H 199/18 than for H 199/19, indicating a lower *in vivo* clearance for H 199/18 than for H 199/19.
- *In vivo*, in normal (rapid) metabolizers, H 199/18 was metabolized more slowly than OME while H 199/19 was metabolized more rapidly. This difference resulted in a higher

AUC of H 199/18 than of omeprazole and, in particular, of H 199/19, after administration of the same dose. This contrast was more evident after repeated dosing than after a single dose, since there was a more pronounced increase in AUC with repeated dosing for H 199/18 than for OME.

- The AUC in poor metabolizers was lower for H 199/18 than for OME. This contributed to overall less interindividual variability for H 199/18 than for OME. For the other enantiomer it was the opposite; the AUC of H 199/19 in poor metabolizers was even higher than that of OME.
- H 199/18 and omeprazole were subject to the same structural transformations in general. Almost complete recoveries were reported. The distribution between urinary and fecal excretion was about 4:1 for both compounds in both poor and extensive metabolizers.
- The increased AUC of H 199/18 with repeated dosing was due to a combination of decreased first pass elimination and decreased systemic clearance, and these parameters were influenced dose-dependently. It appeared that the most pronounced increase in AUC with repeated dosing was from 5 mg to 15 mg and that the dose-dependency from Day 1 to Day 5 in PKs levels out with increasing doses.
- Middle-aged GERD patients exhibited a PK pattern similar to what was obtained in healthy subjects, while elderly subjects had a slightly lower metabolic rate. Subjects with a severe deficit in their liver function had a substantially lower metabolic rate. The PKs of H 199/18 in individuals with impaired renal function was unlikely to differ from healthy individuals.
- A slight gender difference in the PKs of H 199/18 was demonstrated in that the AUC and  $C_{max}$  were slightly higher in Fs than in Ms, but were less different during steady state.
- *In vitro* experiments suggested the following rank order with regard to the potential for metabolic drug-drug interactions *in vivo*; CYP2C19 > CYP2C9 > CYP3A4 = CYP1A2 > CYP2E1 > CYP2D6 > CYP2A6. However, the concentrations needed to achieve an inhibition of these enzymes would probably never be reached in a clinical situation, except for inhibition of CYP2C19.
- *In vivo*, in the drug-drug interaction studies with diazepam, phenytoin and warfarin, it was shown that H 199/18 has potential to inhibit CYP2C19. The slightly inhibited metabolism of cisapride was also suggested to be the result of an inhibition of a minor metabolic pathway for cisapride mediated by CYP2C19.
- H 199/18 did not interact with clarithromycin (two studies) or quinidine, and the slightly increased AUC of cisapride could be explained as an inhibition of CYP2C19. Thus, the

data on these three CYP3A4 substrates indicated that H 199/18 would not have the potential to inhibit this enzyme.

- The minor effects reported for diazepam, phenytoin, warfarin as well as cisapride are all unlikely to be of clinical relevance.
- H 199/18 did not seem to have any potential to interact with drugs that are metabolized by CYP1A2, CYP2A6, CYP2C9, CYP2D6 or CYP2E1.
- As expected, since intragastric pH will increase with H 199/18 treatment, the absorption of drugs with pH sensitive absorption (eg, digoxin, ketoconazole) may be affected.
- Clarithromycin resulted in a doubling of the AUC of H 199/18, but there was no obvious safety issues related to increased plasma levels of H 199/18.
- Food can delay and decrease the absorption of H 199/18, both at single and repeated dosing, and the effect seems more pronounced in Fs than in Ms. **To avoid this food effect, the dose should be taken before a meal.**
- Any inducer of CYP2C19 or CYP3A4 would be predicted to induce the metabolism of H 199/18 resulting in decreased plasma levels.

### **Bioavailability**

- The bioavailability of the phase I/II capsule formulation was 100% relative to that of a solution as tested at 20 mg, and the bioavailability of the phase III capsule was 93% relative to that of the phase I/II capsule as tested at 40 mg.
- The 40 mg market capsule was bioequivalent to the phase III capsule both at single dose and at repeated dose administration under fasting conditions.
- Interim results indicated that the 40 mg market capsule was not bioequivalent to the phase III capsule at single dose administration with food. Final results with 76 subjects will be provided at the 4 month safety update (SU).
- The 20 mg market capsule was bioequivalent to the 20 mg phase III capsule at single dose administration under fasting conditions.

### **5. Brief Summary of Human Pharmacodynamics**

**NOTE:** Some of these PD findings, especially those related to safety, will be reviewed in detail in the Clinical Section of the present review. Once again, the sponsor's conclusions are summarized below because, at this juncture, the PD review is not available.

**a. Mechanism of Action**

- Esomeprazole is a PPI that suppresses gastric acid secretion by highly selective inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase in the gastric parietal cell. By acting specifically on the PP, ESOME Mg blocks the final step in acid production, thus reducing gastric acidity.
- This effect was dose-related and leads to effective control of gastric acid secretion.

**b. Antisecretory Activity**

- The effects of NEXIUM on intragastric pH were compared to OME in 36 patients with symptomatic GERD following repeated administration once daily of 20 and 40 mg capsules over a period of five days. The results are shown in Table 1.

**TABLE 1**  
**NDA 21-153**

**Effects of NEXIUM on Intragastric pH versus OME**

Parameter	NEXIUM (mg)		OME (mg)
	40	20	20
% Times Gastric pH >4 <sup>1</sup>	70%**	53% <sup>1</sup>	44%
Coefficient of variation	26%	37%	52%
Median 24 Hour pH	4.8**	4.1*	3.6
Co efficient of variation	16%	27%	33%

<sup>1</sup> Gastric pH was measured over a 24-h period  
 \* p<0.001 NEXIUM 20 mg vs OME 20 mg  
 \*\* p<0.01 NEXIUM 40 mg vs NEXIUM 20 mg and OME 20 mg

**c. Serum Gastrin Effects**

- The effect of NEXIUM on serum gastrin concentrations was evaluated in ca. 2700 patients in clinical trials up to 8 weeks and in over 1300 patients for up to 6 to 12 months.
- The mean fasting gastrin concentration increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy. [These are not unexpected findings.]

**d. Enterochromaffin-like (ECL) Cell Effects**

- Increased serum gastrin secondary to treatment with antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL hyperplasia in rats and mice and gastric carcinoids in rats, especially in females.

- In over 1000 patients treated with NEXIUM (10, 20 or 40 mg/day) for up to 6 to 12 months, the prevalence of ECL cell hyperplasia increased with time and dose, which is a finding consistent with the pharmacologic action of these antisecretory agents.
- No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.
- Human gastric biopsy specimens have been obtained from more than 3000 patients treated with OME in L-T clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

**e. Endocrine Effects**

- NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks.
- Other effects of NEXIUM on the endocrine system were assessed using OME studies.
- OME given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

**6. Foreign Marketing History**

- Currently, H 199/18 is not approved or marketed in any country.
- \_\_\_\_\_
- From 1988 through 31 January 1999, OME has been approved in 106 countries worldwide.

**II. REQUESTED LABELING FOR THE THREE INDICATIONS SOUGHT**

**INDICATIONS AND USAGE**

[ ]

**Treatment of Gastroesophageal Reflux Disease (GERD)**

Healing of Erosive Esophagitis

Maintenance of Healing of Erosive Esophagitis

Symptomatic Gastroesophageal Reflux Disease

**DOSAGE AND ADMINISTRATION**

The recommended adult dosages are outlined in the table below. NEXIUM Delayed-Release Capsules should be swallowed whole and taken before eating.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The applesauce and the NEXIUM pellets are then swallowed immediately. It is recommended that the applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

**Recommended Dosage Schedule of NEXIUM**

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	—	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	—	Once Daily**
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks

\*\* Clinical trials extended to —  
 \*\*\* If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment should be considered.

**NOTE:** Listed below are the indications for which OME (PRILOSEC) has been approved.

### 1) Duodenal Ulcer (DU)

- Short-term treatment of DU
- In combination with clarithromycin and amoxicillin, OME is indicated for treatment of patients with *H. Pylori* infection and duodenal ulcer disease to eradicate *H. Pylori*.
- In combination with clarithromycin, OME is indicated for treatment of patients with *H. Pylori* infection and duodenal ulcer disease to eradicate *H. Pylori*.

Eradication of *H. Pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL PHARMACOLOGY, Clinical Studies and DOSAGE AND ADMINISTRATION).

Among patients who fail therapy, PRILOSEC with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See Microbiology section, and the clarithromycin package insert, MICROBIOLOGY section.)

### 2) Gastric Ulcer (GU)

PRILOSEC Delayed-Release Capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

### Treatment of Gastroesophageal Reflux Disease (GERD)

#### 3) Symptomatic GERD

PRILOSEC Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

#### 4) Erosive Esophagitis

PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

(See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of PRILOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive

esophagitis or GERD symptoms (e.g. heartburn), additional 4-8 week courses of omeprazole may be considered.

### **5) Maintenance of Healing of Erosive Esophagitis**

PRILOSEC Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

### **6) Pathological Hypersecretory Conditions**

PRILOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

## **III. RATIONALE FOR TESTING THE EFFICACY AND SAFETY OF ESOME Mg AT THE SPECIFIED ONCE-A-DAY DOSES FOR EACH OF THE THREE INDICATIONS SOUGHT**

For a number of years, neutralization of gastric acid with antacids was one of the mainstays for the treatment of GERD. This approach has shifted over the last 15 years from neutralization to inhibition of gastric acid secretion. One primary goal is to decrease the volume and increase the pH of secretions refluxed into the esophagus. The measurement of intraesophageal pH is one of the parameters that may be useful in determining a dose with PD effects to be tested in the treatment of GERD. But, to this reviewer's knowledge, no data from such an evaluation with ESOME Mg have been submitted for review. Instead, as shown in Table 1, there are some data on the effects of NEXIUM vs OME on intragastric pH. This is an indirect and not very precise way of assessing esophageal events. These data do show that in symptomatic GERD patients, following repeated once-a-day administration, both dose levels of NEXIUM chosen, 40 and 20 mg, are significantly better than 20 mg OME. This superiority was shown using either the % time gastric pH >4 (measured over a 24-h period) or the median 24-h pH.

It is not known if there is an optimal degree of acid suppression for healing of EE but very recent publications emphasize the importance of pH control in the management of GERD<sup>17</sup>. There is general agreement among investigators that GERD is associated with dysmotility and eventually results from an imbalance between normal defensive factors (mucosal defense, esophageal clearance, LES tone) and aggressive factors such as acid and pepsin. The goals of treatment are to decrease GER, improve esophageal clearance and protect the esophageal mucosa by, among other things, rendering the refluxate harmless. These goals can be achieved by certain general measures and specific drug treatments. The management of uncomplicated cases generally includes weight reduction, sleeping with the head of the bed elevated by about 4 to 6 in. with blocks, and elimination of factors that increase abdominal pressure. Patients should avoid

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<sup>17</sup> [R.H. Hunt. Importance of pH control in the management of GERD. Arch. Intern. Med. 159:649-657 (1999)]

smoking, fatty foods, coffee, chocolate, alcohol, mint, orange juice, ingestion of large quantities of fluids with meals, and certain medications (such as anticholinergic drugs, calcium channel blockers, and other smooth-muscle relaxants). In mild cases, H<sub>2</sub>-RAs at OTC doses first, then at progressively higher prescription doses, or antacids to neutralize acidity are usually successful.

In moderate to severe cases, the preceding measures are more strictly enforced. H<sub>2</sub> blockers are used in higher doses (cimetidine, 300 mg q.i.d.; ranitidine, 150 mg q.i.d.; famotidine, 20 mg b.i.d.; and nizatidine 150 mg b.i.d.). A protective agent such as sucralfate (1-g chewable tablet, 1 h before meals) is useful in some cases. If the patient does not respond fully, a prokinetic agent such as metoclopramide, 10 mg, 30 min before meals and at bedtime, or cisapride (recently removed from the market) is prescribed to raise LES pressure, hasten gastric emptying, and improve esophageal clearance. The proponents of a specific (exquisite) pH control in the treatment of GERD ignore all the above and claim that it is increasingly clear that the key to control symptoms and to healing EE is to decrease the duration of exposure to acidic refluxate. According to this theory, an intraesophageal pH of <4 directly correlates with the degree of mucosal injury. It is indeed true that the PPIs are significantly more effective than the H<sub>2</sub>-RAs in achieving and sustaining an intragastric pH above 4. Although the premise that before the advent of the PPIs these goals were not attainable is correct, once again, it is not known if intragastric events are accurate surrogates of intraesophageal events. All-in-all, the superiority of the PPIs in controlling 24-h intragastric pH is undisputed. The PPIs appear more effective than H<sub>2</sub>-RAs in attaining a higher intragastric pH and sustaining a pH >4 for a longer duration. But owing to the vagaries of the true significance of changes in esophageal pH, the evidence that one drug is superior to another in either relieving or eliminating symptoms, inducing healing of EE and maintaining healing of esophageal lesions of GERD, must originate from clinical trials.

The sponsor states that omeprazole, the first PPI marketed for clinical use, has been shown to provide effective control of gastric acid secretion over the entire 24-h period [S. Lanzon-Miller et al. *Aliment. Pharmacol. Ther.* 1:239-251 (1987)]. OME has indeed proven very valuable in the treatment of gastric acid-related disorders and has generally been found superior to H<sub>2</sub>-RAs in providing complete symptom resolution and in promoting esophageal healing.<sup>18</sup> Moreover, OME is remarkably well tolerated with relatively few reports of SAEs. Despite its considerable efficacy, OME therapy is not successful in all patients. Healing rates for EE as low as 75% have been reported after 8 weeks of therapy and only about 50% of GERD patients without EE achieve complete symptom resolution after 4 weeks of treatment [J.E. Richter et al. Omeprazole versus ranitidine or ranitidine/metoclopramide in poorly responsive symptomatic gastroesophageal reflux disease. *Amer. J. Gastroenterol.* 91:1766-1772 (1996); PRILOSEC labeling].

But, in the treatment of EE, OME 40 mg was not more effective than OME 20 mg [PRILOSEC labeling]. Thus, there remains a clinical

<sup>18</sup> [K.R. DeVault, D.O. Castell. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Arch Intern Med* 155:2165-2173 (1995)]

[E.C. Klinkenberg-Knol et al. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1:349-351 (1987)]

[S. Sandmark et al. Omeprazole or ranitidine in the treatment of reflux esophagitis. Results of a double-blind, randomized, Scandinavian multicenter study. *Scand J Gastroenterol* 23:625-632 (1988)]

need for a therapeutic agent capable of providing higher healing rates, and which is as safe and well tolerated as OME. Taken together, these considerations appear to provide an acceptable rationale for testing 40 and 20 mg of ESOME Mg given once-a-day and compare these clinical effects to those seen with OME 20 mg per day.

**IV. CRITICAL CLINICAL TRIALS IN NDA 21-153 (TABLE 2)**

In support of the approval of ESOME Mg for each of the three indications being sought, the sponsor has presented information from the following 8 critical trials. The main objectives, primary endpoint of efficacy and other experimental features of the design and proposed execution of these critical clinical trials are summarized in Table 2. Included in this Table, under the column labeled REMARKS are the reviewer's initial assessments of the utility of these critical trials in the formulation of the Division's recommendation for regulatory action. The information in Table 2 must be interpreted in conjunction with the data summarized in Section II. of this review (requested labeling).

Indication →  Proposed Dose (mg)  Proposed Length of Treatment	S-T Healing of EE  40  4 - 8 Weeks	Maintenance of Healing of EE  40  up to 12 months	Primary Symptomatic GERD  20  4 - 8 weeks
Critical Clinical Trials	No. 172 [H40 vs H20 vs O20] (8 weeks)  No. 173 [H40 vs O20] (8 weeks)  No. 174 <sup>a</sup> [H20 vs O20] (8 weeks)  No. 222 [H40 vs O20] (8 weeks)	No. 177 [H40 vs H20 vs H10 vs PL] (6 months)  No. 178 [H40 vs H20 vs H10 vs PL] (6 months)	No. 225 [H40 vs H20 vs PL] (4 weeks)  No. 226 [H40 vs H20 vs PL] (4 weeks)
Supportive Data		No. 179 <sup>b</sup> [H40; no comparator] (12 months)	No. SH-QBE-0008 <sup>c</sup> [H40 vs H20 vs O20] (4 weeks)  No. SH-QBE-0011 <sup>d</sup> [H40 vs O20] (4 weeks)  No. SH-QBE-0021 <sup>e</sup> [H20 vs O20] (4 weeks)
a) This trial will not be reviewed because it did not test the proposed dose of the drug (40 mg) b) This trial, where no comparator was used, will be reviewed for safety only c, d and e) These three trials will not be reviewed because they did not use the same 7-day resolution of heartburn as the critical trials. In addition, study No. SH-QBE-001 did not test the proposed dose of the drug (20 mg).			

TABLE 2  
NDA 21-153

**Main Features of Design and Execution and Initial Assessment of the Utility of the Critical Clinical Trials submitted by the Sponsor in Support of the Approval of the Marketing of ESOME Mg for the Three Indications Sought**

Protocol No. Country	No. of Patients Enrolled Per Gender	Main Features of the Trial	Groups Being Compared	Remarks
172 (US)	M = 1174 F = 785 Total n = 1960	<p><b>I. SHORT-TERM HEALING OF EE</b></p> <p>Randomized, multi-center, double-blind, parallel-group, 3-arm, active controlled</p> <p>Study Population: ca. 1700 patients (560 per arm) with symptomatic endoscopically proven EE</p> <p>Upper G.I. endoscopy at 0, 4 and 8 weeks.</p> <p>The primary endpoint of efficacy was the complete healing of EE (absence of erosions by the Los Angeles classification) induced by H2O or H40 in comparison to O20, each administered q.d. for up to 8 weeks.</p> <p>Secondary questions addressed included whether the same two dose levels of H 199/18 are more efficacious than OME in healing EE at Week 4 and in resolution and relief of symptoms.</p>	<p>All given PO and QD for 8 weeks</p> <p>ESOME Mg (20 mg) [n=656] vs ESOME Mg (40 mg) [n=654] vs OME 20 mg [n=650]</p>	<ul style="list-style-type: none"> <li>Useful design</li> <li>The inclusion of the active comparator (OME at the once-a-day dose of 20 mg, the approved dose of the drug for this indication) is important to demonstrate that ESOME Mg is efficacious. This comparison does not necessarily prove that ESOME is superior to OME.</li> <li>Efficacy of the 40 or 20 mg ESOME Mg is shown by demonstrating statistical superiority of each of these ESOME Mg doses over OME 20 mg.</li> <li>In addition, the large number of patients studied allows dose-response assessments to test the efficacy of the 40 mg in comparison to the 20 mg ESOME Mg dose and choose the best of these two dose levels.</li> </ul>
173 (US)	M = 681 F = 467 Total n = 1148			

<p><b>174</b> <b>(US)</b></p>	<p>M = 748 F = 428 Total n = 1176</p>	<p>Randomized, multicenter, double-blind, parallel-group, 2-arm, active controlled</p>	<p>ESOME Mg (20 mg) vs OME (20 mg)</p>	<ul style="list-style-type: none"> <li>Not useful design because it did not test the proposed dose of the drug (40 mg).</li> <li>This trial will not be reviewed.</li> </ul> <p>(It showed no difference between H20 and O20)</p>
<p><b>222</b> <b>(US)</b></p>	<p>M = 1482 F = 943 Total n = 2425</p>	<p>Randomized, multi-center, double-blind, parallel-group, 2-arm, active controlled.  Study Population: ca. 2425 patients (ca. 1200 per arm) with asymptomatic endoscopically proven EE:  • Study design very similar to that used in Study 172 (see above)</p>	<p>ESOME Mg (40 mg) [n=1,216] vs OME (20 mg) [n=1,209]</p>	<ul style="list-style-type: none"> <li>Useful design.</li> <li>This trial was set to replicate the results in Study 172 (H40 statistically superior to O20) when Study 173 showed to difference between H40 and O20.</li> <li>The inclusion of the active comparator (OMI) at the once-a-day dose of 20 mg, the approved dose of the drug for this indication) is important to demonstrate that ESOME is efficacious. This comparison does not necessarily prove that ESOME is superior to OME.</li> <li>Efficacy of the 40 mg ESOME Mg is shown by demonstrating statistical superiority of this dose of ESOME Mg over the 20 mg dose of OME.</li> </ul>
<p style="text-align: center;"><b>II. MAINTENANCE OF HEALING OF EE</b></p>				
<p><b>177</b> <b>(US)</b></p>	<p>M = 231 F = 144 Total n = 375</p>	<p>Randomized, multi-center, double-blind, parallel-group, 4-arm, placebo-controlled.  Patient Population: Patients with confirmed healing of EE based on endoscopy results at the final visit of Study 172.  Of the healed patients in Study 172, 375 were randomized to double-blind treatment in Study 177.  Endoscopy at Month 1, Month 3 and Month 6 of treatment.  The primary efficacy parameter was the percentage of patients who maintained complete healing of esophagea erosions upon endoscopy evaluation following 6 months of treatment.</p>	<p>All given PO and QD for 6 months  ESOME Mg (10 mg) [n=91] vs ESOME Mg (20 mg) [n=98] vs ESOME Mg (40 mg) [n=92] vs Placebo [n=94]</p>	<ul style="list-style-type: none"> <li>Both trials used the same very useful design.</li> <li>The inclusion of the placebo arm is important to demonstrate that ESOME Mg is shown by demonstrating statistical superiority of this dose level over placebo.</li> <li>Inclusion of three dose levels of the test medication allows a dose-response evaluation thereby permitting a comparison of the effects of low doses (i.e. 10 or 20 mg) vs the highest proposed dose (40 mg) of the drug.</li> </ul> <p style="text-align: right;">(continued on next page)</p>

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<p><b>178 (US)</b></p>	<p>M = 196 F = 122 Total n = 318</p>	<p>Randomized, multi-center, double-blind, parallel-group, 4-arm, placebo-controlled. (Same design as 177)</p> <p>Of the healing patients in Study 172, 318 were randomized to double-blind treatment in Study 178. (Same execution as 177)</p>	<p>ESOME Mg (10 mg) [n=77]</p> <p>vs</p> <p>ESOME Mg (20 mg) [n=82]</p> <p>vs</p> <p>ESOME Mg (40 mg) [n=82]</p> <p>vs</p> <p>PLACEBO [n=77]</p>	<ul style="list-style-type: none"> <li>• By using a second, adequate and well-controlled trial, findings in the other study are properly replicated thus confirming the efficacy of the drug in this indication.</li> <li>• An important particular point when considering the proposed length of treatment for this indication is that the two critical clinical trials were of 6-month duration but the sponsor is requesting up to _____ administration of the drug.</li> </ul>
<p><b>III. SYMPTOMATIC GERD (s-GERD)</b></p>				
<p><b>225 (US)</b></p>	<p>M = 143 F = 225 Total n = 368</p>	<p>Randomized, multi-center, double-blind, parallel-group, 3-arm, placebo-controlled.</p> <p><u>Study Population</u> Patients who identified HB as their primary symptoms had a Hx of HB episodes for 6 months or longer, experienced HB on at least 4 of the 7 days preceding the baseline visit and showed macroscopically normal esophageal mucosa at the screening endoscopy.</p> <ul style="list-style-type: none"> <li>• Severity of HB assessed at baseline and at Week 2 and Week 4.</li> <li>• The primary efficacy parameter was the percentage of patients with complete resolution of HB (7-day resolution of HB by diary).</li> </ul>	<p>All given PO and QD for 2 Weeks</p> <p>ESOME Mg (20 mg) [n=121]</p> <p>vs</p> <p>ESOME Mg (40 mg) [n=123]</p> <p>vs</p> <p>PLACEBO [n=124]</p> <p>ESOME Mg (20 mg) [n=113]</p> <p>vs</p> <p>ESOME Mg (40 mg) [n=118]</p> <p>vs</p> <p>PLACEBO [n=118]</p>	<ul style="list-style-type: none"> <li>• Both trials used the same very useful design.</li> <li>• The inclusion of the placebo arm is important in demonstrate that ESOME Mg (any dose) is efficacious</li> <li>• Efficacy of the proposed 20 mg dose of ESOME Mg is shown by demonstrating statistical superiority of this dose level over placebo.</li> <li>• The inclusion of an arm with twice the amount of drug as that of the proposed dose allows an evaluation of whether doses higher than the proposed may be accompanied with a higher benefit.</li> <li>• By using a second, adequate and well-controlled trial, findings in the other study are properly replicated thus confirming the efficacy of the drug in this indication.</li> </ul>
<p><b>226 (US)</b></p>	<p>M = 126 F = 223 Total n = 349</p>	<p>Randomized, multi-center, double-blind, parallel group, 3-arm, placebo-controlled. (Same design as 225) (Same execution as Study 225)</p>	<p>ESOME Mg (20 mg) [n=113]</p> <p>vs</p> <p>ESOME Mg (40 mg) [n=118]</p> <p>vs</p> <p>PLACEBO [n=118]</p>	<p>ESOME Mg (20 mg) [n=113]</p> <p>vs</p> <p>ESOME Mg (40 mg) [n=118]</p> <p>vs</p> <p>PLACEBO [n=118]</p>

## **V. REVIEW OF CLINICAL TRIALS FOR THE INDICATION SHORT-TERM HEALING OF EROSIVE ESOPHAGITIS**

### **A. Study 172**

*"A Multicenter, Randomized, Double-blind, Eight Week Comparative Efficacy and Safety Study of H 199/18 20 mg, H 199/18 40 mg and Omeprazole 20 mg in Study Subjects with Erosive Esophagitis"*

#### **1. Primary Objective**

To assess the efficacy, defined as complete healing of erosive esophagitis, of H 199/18 20 mg q.d. and H 199/18 40 mg q.d. compared to omeprazole 20 mg q.d. at Week 8 of treatment in subjects with erosive esophagitis.

#### **2. Secondary Objectives**

To assess the following:

- Efficacy, defined as complete healing of erosive esophagitis, of H 199/18 20 mg q.d. and H 199/18 40 mg q.d. compared to OME 20 mg q.d. at Week 4 of treatment.
- Efficacy, defined as complete healing of erosive esophagitis, of H 199/18 20 mg q.d. compared to H 199/18 40 mg q.d. at Week 4 and Week 8 of treatment.
- Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H 199/18 20 mg q.d. and H 199/18 40 mg q.d. compared to OME 20 mg q.d. at Week 4 and Week 8 of treatment.
- Time to resolution and relief of heartburn by H 199/18 20 mg q.d. and H 199/18 40 mg q.d. compared to OME 20 mg q.d.
- Safety and tolerability of H 199/18 20 mg q.d. and H 199/18 40 mg q.d. compared to OME 20 mg q.d.

**COMMENT:** The approaches/procedures to achieve these primary and secondary objectives were all adequate.

#### **3. Study Population (Table 3)**

This was adequate for this type of study. The study population consisted of ca. 1700 patients with symptomatic erosive esophagitis (EE) at ca. 150 clinical investigational centers in the U.S. Listed in Table 3 are: a) criteria for randomization of EE patients into the trial; and b) the criteria used to exclude patients from participation in this study.

**TABLE 3**  
**Study No. 172**  
**Characteristics of the Study Population**

INCLUSION CRITERIA	REASONS FOR EXCLUSION												
<ul style="list-style-type: none"> <li>Adults 18 to 75 y of age inclusive (and of legal age to consent).</li> <li>Ms or non-pregnant, non-lactating Fs. Females must be postmenopausal, surgically sterilized or using an acceptable form of birth control as determined by the investigator. Women of child bearing potential must agree to continue using an acceptable form of birth control throughout the conduct of the study.</li> <li>All women of child-bearing potential (i.e., those not postmenopausal or surgically sterilized) must have a negative pregnancy test at baseline.</li> <li>EE, confirmed by EGD using the LA Classification, within one week prior to study randomization.</li> </ul> <p><b>Los Angeles Classification of esophagitis:</b></p> <table border="1"> <thead> <tr> <th style="text-align: left;">Classification</th> <th style="text-align: left;">Definition</th> </tr> </thead> <tbody> <tr> <td>Not Present</td> <td>No breaks (erosions) in the esophageal mucosa. (However, edema, erythema or friability may be present).</td> </tr> <tr> <td>Grade A</td> <td>One or more mucosal breaks not more than 5 mm in maximum length</td> </tr> <tr> <td>Grade B</td> <td>One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds</td> </tr> <tr> <td>Grade C</td> <td>Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference</td> </tr> <tr> <td>Grade D</td> <td>Mucosal breaks which involve at least 75% of the esophageal circumference</td> </tr> </tbody> </table> <p>*Definitions derived from D. Armstrong et al.</p> <ul style="list-style-type: none"> <li>Subjects capable of providing written IC, willing and able to comply with all procedures of the trial.</li> </ul>	Classification	Definition	Not Present	No breaks (erosions) in the esophageal mucosa. (However, edema, erythema or friability may be present).	Grade A	One or more mucosal breaks not more than 5 mm in maximum length	Grade B	One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds	Grade C	Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference	Grade D	Mucosal breaks which involve at least 75% of the esophageal circumference	<ul style="list-style-type: none"> <li>Positive for <i>H. pylori</i> by serology at baseline</li> <li>Any bleeding disorder or signs of GI bleeding at the time of the baseline EGD or within 3 days prior to randomization</li> <li>History of gastric or esophageal surgery, except for simple closure of perforated ulcer.</li> <li>Current or historical evidence (within 3 months) of the following diseases/conditions: Zollinger-Ellison syndrome, the primary esophageal motility disorders achalasia, scleroderma, and/or primary esophageal spasm, esophageal stricture, IBD, evidence of UGI malignancy at the baseline EGD, pancreatitis, malabsorption, severe cardiovascular or pulmonary disease, severe liver disease<sup>a</sup>, severe renal disease, including chronic renal disease or impaired renal function<sup>b</sup>, active malignant disease except minor superficial skin disease, unstable diabetes mellitus<sup>c</sup>, cerebral vascular disease<sup>d</sup>, any condition that may require surgery during the study.</li> <li>Endoscopic Barrett's esophagus (&gt;3 cm) or significant dysplastic changes in the esophagus.</li> <li>Known clinically significant abnormal laboratory values as part of their medical history.<sup>e</sup></li> <li>Use of PPI within 28 days prior to the baseline visit.</li> <li>Use of daily H<sub>2</sub>-receptor antagonist during the two weeks prior to the baseline EGD<sup>f</sup>.</li> <li>Need for continuous concurrent therapy or treatment within one week of randomization with: diazepam, quinidine, diphenylhydantoin, mephenytoin, warfarin, anticholinergics, prostaglandin analogs, antineoplastic agents, salicylates (unless ≤165 mg daily for cardiovascular prophylaxis), steroids (oral or intravenous), pro-motility drugs, sucralfate, nonsteroidal anti-inflammatory drugs.</li> <li>Known hypersensitivity to any component of H 199/18, Prilosec® (omeprazole) or Gelusil®.</li> <li>Use of any other investigational compound within 28 days of starting test medication.</li> <li>History of drug addiction or alcoholism within the past 12 months.</li> <li>Refusal to sign the IC or inability to give fully IC due to mental deficiency or language problems.</li> <li>Prior participation in this study or another clinical study of H 199/18.</li> <li>Prior participation in this study or another clinical study of H 199/18.</li> <li>Inability to take test medication according to dosing instructions.</li> <li>Pregnancy or lactation.</li> </ul>
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<p><b>Reviewer's Table</b></p> <p><b>Abbreviations used:</b> M=male; F=female; EE=erosive esophagitis; EGD=esophagogastroduodenoscopy; IC=informed consent; GI=gastrointestinal; Z-E=Zollinger-Ellison; IBD=inflammatory bowel disease; UGI=upper gastrointestinal; PPI=proton pump inhibitor.</p> <p><sup>a</sup> Subjects with liver enzymes 3 times the ULN were to be excluded from study participation.</p> <p><sup>b</sup> As manifested by the following: Cr clearance &lt;50 mL/min, serum creatinine &gt;2.0 mg/dL or markedly abnormal urine sediment on repeated examinations.</p> <p><sup>c</sup> Stable diabetics controlled on diet, oral agents or insulin were acceptable.</p> <p><sup>d</sup> Such as cerebral ischemia, infarction, hemorrhage or embolus.</p> <p><sup>e</sup> These were to be reviewed and discussed with the Medical Monitor</p> <p><sup>f</sup> Occasional use less than daily was to be permitted</p>													

#### 4. Overall Study Design and Schedule of Evaluations

From the review of the evidence, this was a multi-center, randomized, double-blind, 3-arm, parallel-trial that investigated the efficacy of ESOME Mg (20, 40 mg once-a-day) in comparison to OME 20 mg once daily in patients with patients with symptomatic EE. The allocation to treatment was 1:1:1 with respect to the number of patients that received test medication or active comparator. Gelusil® (antacid) tablets were dispensed as a rescue medication to be utilized by patients for relief of GERD symptoms up to a maximum of 6 tablets per day. The initially planned total enrollment was ca. 1700 patients; instead 1960 were enrolled; of these, 1801 completed the trial (see below).

In Table 4, a checklist of clinical and laboratory measurements is given. Randomized into this trial (and study 173) were patients that had endoscopically demonstrated EE, grade A through D in the Los Angeles classification of esophagitis, and mostly symptomatic (2 to 3% of the enrolled patients did not have heartburn). All in all, there were 3 visits (at Weeks 0, 4 and 8 or final) and 3 endoscopies [at initial visit (Day -1), visit 2 (Day 28 ± 4 Days) and visit 3 (Day 56 ± 4 days)]. Final efficacy and safety determinations were to be made for all patients with endoscopic evidence of healing to the "NOT PRESENT: grade of the Los Angeles classification of esophagitis [No breaks (erosions) in the esophageal mucosa] at study Week 4 or 8 or in the last day they took a full dose of test medication. Heartburn (HB) was assessed daily each morning during the first 4 weeks of treatment. The patients were instructed to register the severity of their most severe HB episode. Diary card entries made by the patients were for the 24-h period prior to that morning's test medication dose. The patients were also asked to indicate if nocturnal HB was present. The (adequate) definitions of HB and its severity are reproduced below.

**Heartburn:** A burning feeling, rising from the stomach or lower part of the chest towards the neck.

**Severity:** The most intense episode over previous 24 h to be classified as none (no symptoms), mild, moderate or severe as follows:

<b>None:</b>	No heartburn
<b>Mild:</b>	Awareness of HB, but easily tolerated
<b>Moderate:</b>	Discomforting HB sufficient to cause interference with normal activities (including sleep)
<b>Severe:</b>	Incapacitating HB, with inability to perform normal activities (including sleep)

- Assessment of symptoms were completed by the investigator on each subject at baseline, Week 4 and Week 8. The GERD symptoms of HB, acid regurgitation, dysphagia, and epigastric pain were assessed for the 7 days prior to the visit and documented on the CRF. The assessment included the severity of the most intense episode within the past week.
- Patients could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event (AE), or for other reasons unrelated to treatment. Patients withdrawn from the trial were not replaced.