CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

STATISTICAL REVIEW(S)

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

NDA#: 21-154
Serial Number: 000
Type: Original Application
Date of Submission: 2/28/00

Review Division: Special Pathogen and Immunologic Drug Products
HFD-590
Reviewer: Stephen G. Hundley, Ph.D., Pharmacologist
Review Completion Date: 10/31/00

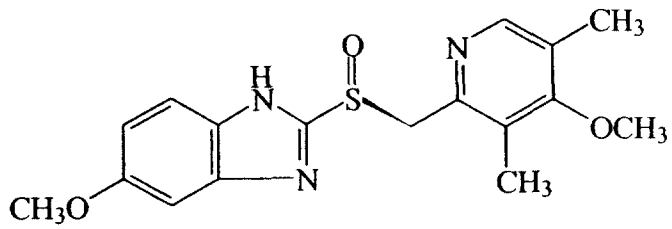
Sponsor: AstraZeneca LP
725 Chesterbrook Blvd.
Wayne, PA 19807-5677
Phone: 610-695-1008

Drug Information

Name: Esomeprazole (S-Omeprazole or H 199/18)
Drug Name: Nexium™ (Esomeprazole magnesium)
Chemical Name: Bis (5-methoxy-2-[(S)-[(4-methoxy-3.5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole-1-yl) magnesium salt

Free base: 5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole-1-yl

CAS#'s: 217087-09-7 (Magnesium trihydrate)
73590-58-6 (Free base)
Molecular Formula: $(C_{17}H_{18}N_3O_3S)_2$ Mg • $3H_2O$ (Magnesium trihydrate)
$C_{17}H_{19}N_3O_3S$ (Free base)
Molecular Weight: 767 (Magnesium trihydrate), 345.4 (Free base)
Molecular Structure: Free Base



S-Omeprazole (Esomeprazole)

Drug Category: Parietal cell proton pump inhibitor

Related Submissions: IND's: [redacted]
NDA's: 20-916; 19-810; and 21-153

Proposed Indication: Eradication of *Helicobacter pylori* in the treatment of [redacted] ulcers [redacted] in combination therapy with amoxicillin (1g, bid) and clarithromycin (500 mg, bid).

BACKGROUND

Omeprazole, marketed as Prilosec®, is approved for use as therapy for gastroesophageal reflux disease and erosive esophagitis. Secretion of gastric acid from parietal cells is blocked due to the inhibition by omeprazole of the H+/K+ ATPase enzyme (proton pump). Omeprazole is a racemic mixture of the R- and S-enantiomers with both enantiomers exhibiting proton-pump inhibition activity. Omeprazole in combination with the antibiotics clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) was evaluated and approved as a 14-day dosing regimen for *Helicobacter pylori* eradication. Numerous literature citations indicated combined acid supression/antimicrobial therapy was more effective against *H. pylori* than antimicrobial therapy alone. Increased gastric pH evidently enhanced the effect of antimicrobials against *H. pylori*.

In the current submission the sponsor evaluated the clinical efficacy of the S-enantiomer of omeprazole as the magnesium salt (esomeprazole magnesium) in combination therapy with clarithromycin and amoxicillin for eradication of *H. pylori*. The evaluated dosing regimen was 40 mg of esomeprazole magnesium (Nexium™) with clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) for a period of ten days.

The sponsor previously submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) an NDA package (NDA 21-153; 12/3/99 submission date) on esomeprazole magnesium for the treatment of gastroesophageal reflux disease and erosive esophagitis. The nonclinical pharmacology/toxicology reports contained in NDA 21-153 were evaluated and the Pharmacologist's Review was completed on 8/8/00. The current Pharmacology/Toxicology Review relies upon evaluations and conclusions of the Pharmacology Reviewer from HFD-180. The nonclinical pharmacology/toxicology studies submitted to NDA 21-153 are listed in the following section.

NONCLINICAL STUDIES

Expert Report on Omeprazole Toxicological and Pharmacological Documentation.

Addendum to Expert Report on Omeprazole Toxicological and Pharmacological Documentation.

Gastric Acid Secretion after a Single Dose of Omeprazole Sodium, H 199/18 Sodium, or H 199/19 Sodium in Female Rats (Report Number 3222-0353).

Effect of Omeprazole and Its Enantiomers on Acid Formation in Isolated Glands (Report Number 222-0123-00).

Pharmacokinetic Study of Omeprazole Sodium, H 199/18 Sodium, and H 199/19 Sodium Following Single Intravenous and Intraduodenal Administration in the Rat (Report Number 3222-0336).

Pharmacokinetic Study of Omeprazole and H 199/18 Magnesium Following Repeated Oral Administration in the Dog (Report Number 23870).

Excretion and Metabolism of H 199/18-^{14}C in Dogs after Oral Administration – A Comparison with [^{14}C] Omeprazole (Report Number 23992).

Study of any *In Vivo* Racemization of H 199/18 and H 199/19 in the Rat (Report Number 3222-0320).

Comparison of the Single Dose Toxicity of H 199/18 Sodium, H 199/19 Sodium, and Omeprazole Sodium in Rats after Oral Administration (Report Number T2816).

Comparison of the General Toxicity of H 199/18 Sodium, H 199/19 Sodium, Omeprazole Sodium, and Omeprazole Given Orally to Rats for 1 Month (Report Number T2823).

Toxicokinetics and Thyroid Hormone Levels after 1 Month's Oral Administration of H 199/18 Sodium, H 199/19 Sodium, Omeprazole Sodium, and Omeprazole in Rats (Report Number T2822).

H 199/18 Magnesium: Three-month Oral General Toxicity Study in Wistar Rats – A Comparison with Omeprazole (Report Number SR97477-01).

H 199/18 Magnesium: 3 Month Oral (Gavage) Toxicity in the Dog – A Comparison with Omeprazole Magnesium (Report Number SR97103 – 01).

H 199/18 Magnesium: Oral Dose Finding Embyro-Fetal Development Study in the Rat, A Comparison Study with Omeprazole (Report Number SR97207-01).

H 199/18 Magnesium: Oral Embryo-Fetal Development Study in the Rat, a Comparison with Omeprazole (Report Number 97469-01).

H 199/18 Magnesium: Oral Dose Finding Embryo-Fetal Development in the Rabbit, A Comparison Study with Omeprazole (SR97325-01)

H 199/18 Magnesium: Effects in pregnant Rabbits and a Toxicokinetic Evaluation When Given Orally (Report Number SR98107).

H 199/18 Magnesium: Effects on Pregnant Rabbits and a Toxicokinetic Evaluation after Oral Administration (Report Number SR98344-02).

H199/18 Magnesium: Oral Embryo-Fetal Development Study in the Rabbit. A comparison with Omeprazole (Report Number SR98498-01).

Mutagenicity Evaluation of H 199/18 Sodium in the Ames Salmonella/Mammalian Microsome Mutagenicity Test (Report Number T2817).

H 199/18 Magnesium: In Vitro Cytogenetic Test Using Human Peripheral Blood Lymphocytes (Report Number SR98045-01).

H 199/18 Magnesium and Omeprazole: Comparison of Solubilities (Report Number SR98232-01).

Mouse Micronucleus Test of H 199/18 Magnesium Given by Gavage (Report Number SR97484-01).

H 199/18 Magnesium: Induction of Chromosome Aberrations in the Bone Marrow of Treated Rats (Report Number SR98457-01).

Omeprazole Magnesium: Pharmacological-Toxicological Expert Report (Report Number 97164-7).

EVALUATION AND CONCLUSIONS

The sponsor submitted several repeat-dose toxicity studies comparing H 199/18 (S-omeprazole), H 199/19 (R-omeprazole), and omeprazole (racemate). The Pharmacology/Toxicology Review from HFD-180 indicated that each test compound produced equivalent toxicological effects in each of two strains of rats and in beagle dogs. The toxicity from esomprazole magnesium (the magnesium trihydrate of S-omeprazole) was shown to be equivalent to omeprazole in 3-month oral dosing studies in Wistar rats and beagle dogs. Esomeprazole magnesium (H 199/18 magnesium) was also evaluated in embryo-fetal development studies (Segment II reproductive toxicity) in rats and rabbits. Results from these studies were in agreement with prior results obtained with omeprazole. Finally, the results from a battery of genetic toxicology studies with esomprazole magnesium were in agreement with results obtained in prior submissions with omeprazole.

The comprehensive review conducted by the Pharmacology/Toxicology Reviewer in HFD-180 indicated that esomeprazole magnesium was toxicologically equivalent to omeprazole. Consequently, the Reviewer had no safety concerns with an oral dosing

regimen of 40 mg Nexium™ administered daily for a period of time up to eight weeks for treatment of gastroesophageal reflux disease or erosive esophagitis. The proposed dosing regimen for eradication of *Helicobacter pylori* in the current NDA includes 40 mg of Nexium™ daily for a period of 10 days. There are no nonclinical safety concerns with regard to this Nexium™ dosing regimen. The proposed daily dosing regimens for clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) for a period of ten days are consistent with currently approved dosing regimens for these two drug products. The proposed triple therapy dosing regimen is also consistent with the currently approved triple therapy dosing regiment for Prilosec® (omeprazole).

KEYWORDS: Esomeprazole, Proton Pump Inhibitor, *Helicobacter pylori*, Nonclinical Toxicology

/S/ 10/31/00
Stephen G. Hundley, Ph.D.

Concurrences:
HFD-590 / R.Albrecht / DDDir /S/ 11/1/2000
HFD-590 / K.Hastings / TL 11/3/00

Disk:
HFD-590 / K.Hastings

cc:
HFD-590 / Original IND
HFD-590 / Division File
HFD-345
HFD-590 / CSO / J.Fritsch
HFD-590 / MO / R.Roca
HFD-590 / Pharm / S.Hundley
HFD-590 / Chem / G.Holbert
HFD-590 / Micro / P.Dionne
HFD-590 / Biopharm / J.Meyer
HFD-590 / Stat / K.Higgins

NDA Statistical Review and Evaluation (Clinical)

OCT 3 2000

NDA#:	**21- 153**
Drug Name:	**Nexium™ (Esomeprazole Magnesium H199/18)**
Drug Class:	**1S**
Sponsor:	**AstraZeneca LP, Wayne, PA**
Date Submitted:	**December 3, 1999**
User Fee Date:	**October 3, 2000**
Formulation/ Route of Administration:	**Delayed-Release Capsule for Oral Administration**
Proposed Indication:	**a) Healing of Erosive Esophagitis (EE) b) Maintenance of Healing of (EE) c) Treatment of Symptomatic Gastroesophageal Reflux Disease (s-GERD)**
Martial Reviewed:	**The statistical sections of total of 359-volume submission, plus the statistical sections of 31 volumes of item 8**
Statistical Reviewer:	**Yi Tsong, Ph.D., Mathematical Statistician, HFD-705**
Chemical Reviewer:	**Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, HFD-180**

I. INTRODUCTION

NEXIUM™ (defined in clinical trial as H199/18 and abbreviated in this review as H), is a gastric acid anti-secretory substituted benzimidazole. NEXIUM™, intended for oral administration, is available as delayed capsules. The sponsor submitted the following four groups of clinical trials that evaluated the efficacy and safety of NEXIUM in the treatment of the GERD-related indications for which approval is being sought. To be more specific, the claims are

1) Healing of erosive esophagitis
2) Maintenance of healing of erosive esophagitis
3) Treatment of symptomatic GERD

Esomeprazole magnesium is the s-enantiomer of PRILOSEC (omeprazole, abbreviated in this review as O). PRILOSEC has been approved for many conditions including short-term treatment of duodenal ulcer, 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 long-term treatment of pathological hypersecretory conditions. Hence, PRILOSEC 20 mg was chosen as the active control in most of the clinical trials.

There were four active controlled clinical trials in healing of erosive esophagitis:
Study 172 [H40 mg (n=654) vs H20 mg (n=656) vs. O20 mg (n=650)]
Study 173 [H40 mg (n=576) vs O20 mg (n=572)]
Study 174 [H20 mg (n=588) vs O20 mg (n=588)]

Study 222 [H40 mg (n=1,216) vs O20 mg (n=1,209)]
All 4 studies were considered pivotal by the FDA medical reviewer.

There were two placebo controlled clinical trials in maintenance of healing of erosive esophagitis. Both studies were considered pivotal.

Study 177 [H40 mg (n=92) vs H20 (n=98) vs H10 mg (n=91) vs PL (n=72)]
Study 178 [H40 mg (n=82) vs H20 (n=82) vs H10 mg (n=77) vs PL (n=118)]

There were five controlled clinical trials in the treatment of s-GERD. Of these, two were placebo-controlled studies and were considered pivotal by FDA medical reviewer.

Study 225 [H40 mg (n=123) vs H20 mg (n=121) vs PL (n=124)]
Study 226 [H40 mg (n=118) vs H20 mg (n=113) vs PL (n=118)]

The three supportive trials used O20 as active control.

Study SH-QBE-0009 [H40 mg (n=425) vs H20 mg (n=423) vs O20 mg (n=434)]
Study SH-QBE-0011 [H40 mg (n=347) vs O20 mg (n=346)]
Study SH-QBE-021 [H20 mg (n=336) vs O20 mg (n=334)]

As shown in following sections, all of these studies were well-designed double-blind, randomized, with appropriate controls, patient populations and consistent inclusion and exclusion criteria.

In addition, there was one non-comparative long-term clinical trial, Study 179, which provided supportive information on the effectiveness of H199/18 in the maintenance of healing of EE.

The statistical review of this NDA is presented in four sections. The review of the four clinical trials submitted in supporting of treatment for "healing of erosive esophagitis" is given in Section II. The review of the two clinical trials submitted in supporting of the treatment for "maintenance of healing of erosive esophagitis" is given in Section III. The review of the five clinical trials in supporting of treatment of symptomatic GERD is given in Section IV. The integrated summary of efficacy and safety of H188/19 for the three indications is given in Section V, the last section.

II. SHORT-TERM HEALING OF EROSIVE ESOPHAGITIS

II.A STUDY 172

Study 172 was a multicenter, randomized, double-blind, eight week comparative efficacy and safety study of H199/18 20 mg, H199/18 40 mg and omeprazole 20 mg in subjects with erosive esophagitis.

The primary objective of the study is complete healing of erosive esophagitis of H40 mg q.d. and H20 mg q.d. compared to omeprazole 20 mg q.d. at week 8 of treatment.

The secondary objectives are

1. Efficacy, defined as complete healing of erosive esophagitis, of H40 mg q.d. and H20 mg q.d., compared to OME 20 mg at week 4 of treatment.
2. Efficacy, defined as complete healing of erosive asophagitis, of H20 mg q.d., compared to H40 mg at week 4 and week 8 of treatment.
3. Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H40 mg q.d. and H20 mg q. d. as compared with OME 20 mg q.d. at week 4 and week 8 of treatment.
4. Time to resolution and relief of heartburn of H20 mg q.d. and H40 mg q.d, as compared to OME 2o mg q.d.
5. Safety and tolerability of H20 mg q.d. and H40 mg q.d., as compared to OME 20 mg q.d.

The study population consists of 1700 patients (adults 18 to 75 of age) with symptomatic erosive esophagitis (EE) enrolled at 150 centers in the U.S.

The sample size of 500 patients per treatment arm was calculated based on having 95% power to detect a 10% difference in complete healing rate of 85% for each dose of H 199/18 and 75% of OME 20 mg. The sample size calculated was performed using arcsine transformation, for a two-sided test, with Bonferroni correction for two comparisons (i.e. corrected type I error rate of 0.025).

Randomization was performed at each center.

The assessment of symptoms was completed by the investigator on each subject at baseline, Week 4 and Week 8. The GERD symptoms of heartburn (HB), acid regurgitation, dysphagia, and epigastric pain were assessed for the 7 days prior to the visit. Details of the study flowchart of clinical and laboratory measurements are given in Table II.A.1.

Table II.A.1 Study Flowchart of Clinical and Laboratory Measurements

Procedure	Baseline	Week 4	Week 8
	Day-1	Day 28 ±4days	Day 56±4 days
Informed Consent	x		
Medical History	X		
Physical Examination	x		x
Vital Signs	x	X	x
Laboratory Samples	x		x
H Pylori Serology Screening	x		
EGD	x	X	x
Gastric Biopsy	x		
Pregnancy Test	x		
Dispense Diary Card	x		
Review Diary Cards		X	x
GERD Symptom Assessment	x	X	x
Adverse Event Assessment		X	x
Review Concomitant Medications	x	X	x
Dispense Study Drug	x	X	
Drug Accountability		X	X
End of Safety Status			X

Analysis Population: Patients participated could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event, or for other reasons unrelated to treatment. Distribution of randomization and disposition of patients entered into trial are given in the following Table 2. The ITT population included all patients randomized to treatment, with no exclusion. In the PP population, patients excluded because of study exclusion criteria, compliance violations, prohibited concomitant medications, etc. The percentage of exclusion in PP population was 28.3% and was evenly distributed among the three treatment groups.

Table II.A.2 Distribution and Disposition of Patients Entered into Study 172

Screened N=3354				
Not Enrolled = 1394				
	H 199/18 40 mg	H199/18 20 mg	OME 20mg	Total
Randomized (ITT Population)	654	656	650	1960
Week 4				
Completed	465	436	399	1300
Ongoing	146	183	219	546
Discontinued	43	38	33	114
Week 8				
Completed	143	175	208	526
Discontinued	3	8	11	22
Safety Population (Rec'd at least 1 dose)	653	655	649	1957
PP Population	536	550	534	1620
Patient Evaluability				
ITT Population	654	656	650	1960
Patients with Week 4 Endoscopy	618	621	622	1861
Patients with Week 8 Endoscopy	139	171	204	514
PP Population	536	550	534	1620
Patients with Week 4 Endoscopy	535	550	534	1619
Patients with Week 8 Endoscopy	128	160	161	469

Baseline measurements: The three treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – In ITT population, at Week 8, the complete healing proportions were 87.6%, 83.8% and 81.4% of patients treated with H40 mg q.d., H20 mg q.d. and OME 20 mg q.d. respectively. The targeted therapeutic gain of 10% at Week 8 was not achieved in either H40 mg q.d. or H20 mg q.d. However, H40 mg q.d. group had a statistically significantly higher healing proportion than OME 20 mg q.d. using either log-rank test, Wilcoxon test or CMH test with 2-sided p-value <0.025 (Table II.A.3). On the other hand, the proportion of healing of H20 mg q.d. group was not statistically significantly higher than that of OME 20 mg q.d. (p>0.025)..

The secondary objectives -

1. H40 mg q.d. group had a 9.7% higher healing proportion than OME 20 mg q.d. group at week 4 of treatment. The difference was statistically significant with p <0.001 using CMH test. However, H20 mg q.d. group had 5.1% healing proportion higher than OME 20 mg q.d. group and the difference was statistically significant (Table II.A.3).

2. H40 mg q.d., group had 4.6% higher healing proportion at Week 4 and 3.8% higher healing proportion at Week 8 than H20 mg q.d. group. The difference was not statistically significant at either only statistically significant at Week 8 using Log-rank test unadjusted for multiple comparisons (p=0.035).

Table II.A.3 EE Healing Proportion of the Treatment Groups in Study 172

Week	H40 mg	H20 mg	OME 20 mg	H40 mg vs OME 20 mg[a]	H20 mg vs OME 20 mg[a]	H40 mg vs H20 mg[b]	Stat Test
n	654	656	650				
4	465 (71.1%)	436 (66.5%)	399 (61.4%)	9.7% <0.001	5.1% N.S.	4.6% N.S.	CMH
8	573 (87.6%)	550 (83.8%)	529 (81.4%)	6.2% <0.001* <0.001* 0.003*	2.4% 0.042 N.S. N.S.	3.8% 0.035 N.S. N.S.	Log-rank Wilcoxon CMH

a: From sponsor's analysis
b: Reviewer's analysis with unadjusted p-value.
*: Statistically significant with p-values adjusted for multiple comparisons (Hochberg).

3. Results of complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain at Week 4 and Week 8 are shown in Table II.A.4 and Table II.A.5. The only difference was in heartburn resolution proportion at Week 4 between H40 mg and OME 20 mg.

Table II.A.4 Proportion of Patients of Investigator-Recorded Complete Resolution of GERD Symptoms at Week 4 and Week 8

Treatment	n	Week 4		Week 8	
		Proportion	p-value*	proportion	p-value*
Heartburn					
H40 mg q.d.	621	64.7%	0.005	60.4%	N.S.
H20 mg q.d	626	61.0%	0.171	59.1%	N.S.
OME 20 mg q.d.	624	57.2%	--	57.1%	--
Regurgitation					
H40 mg q.d.	621	77.1%	0.152	75.0%	N.S.
H20 mg q.d	626	74.9%	0.513	71.6%	N.S.
OME 20 mg q.d.	624	73.6%	--	74.1%	--
Dysphasia					
H40 mg q.d.	621	91.3%	0.630	88.9%	N.S.
H20 mg q.d	626	89.6%	0.110	90.3%	N.S.
OME 20 mg q.d.	624	92.1%	--	92.9%	--
Epigastric Pain					
H40 mg q.d.	621	76.8%	0.087	83.3%	N.S.
H20 mg q.d	626	79.1%	0.506	79.5%	N.S.
OME 20 mg q.d.	624	81.3%	--	82.5%	--

Modified from sponsor's Tables 14.2.13 and 14.2.14
* CMH test, Compared with OMS 20 mg.

Table II.A.5 Proportion of Patients of Investigator-Recorded Relief of GERD Symptoms at Week 4 and Week 8

Treatment	n	Week 4		Week 8	
		Proportion	p-value*	Proportion	p-value*
Heartburn					
H40 mg q.d.	621	89.2%	0.343	90.3%	N.S.
H20 mg q.d	626	88.3%	0.736	88.6%	N.S.
OME 20 mg q.d.	624	87.7%	--	88.9%	--
Regurgitation					
H40 mg q.d.	621	93.91%	0.627	91.7%	N.S.
H20 mg q.d	626	92.3%	0.581	92.0%	N.S.
OME 20 mg q.d.	624	93.3%	--	92.5%	--
Dysphasia					
H40 mg q.d.	621	97.6%	0.896	97.9%	N.S.
H20 mg q.d	626	97.8%	0.976	96.6%	N.S.
OME 20 mg q.d.	624	97.8%	--	98.1%	--
Epigastric Pain					
H40 mg q.d.	621	93.68%	0.389	95.8%	N.S.
H20 mg q.d	626	92.5%	0.111	96.0%	N.S.
OME 20 mg q.d.	624	95.2%	--	92.9%	--

Modified from sponsor's Tables 14.2.15 and 14.2.16
* CMH test, Compared with OMS 20 mg.

4. There is statistical difference in time to resolution and relief of heartburn of H40 mg q.d, as compared to OME 20 mg q.d. H40 mg q.d. had shorter time to first resolution ($p=0.013$) and short time to first relief ($p<0.001$) of heartburn symptom than OME 20 mg q.d. There was no difference between H20 mg q.d. and OME 20 mg q.d.

Efficacy by Subgroups -
There was no meaningful difference in healed proportion of patients between male and female, between patients in <65 years old age group and ≥ 65 years old age group or among the races (Caucasian, Black, Asian and Others) (Table II.A.6).

The proportion of patients healed at Week 4 was greater for *H. pylori* positive patients than for *H. pylori* negative patients. At Week 8, there was no meaningful difference between the two groups (Table A.II.6).

Table II.A.6 Healing of EE by Subgroups, Study 172

	Treatment	n	Week 4	Week 8
			Proportion	Proportion
Proportion of Patients Healed by Gender				
Male	H40 mg q.d.	384	70.3%	87.5%
	H20 mg q.d	391	65.7%	82.9%
	OME 20 mg q.d.	399	59.1%	79.2%
Female	H40 mg q.d.	270	72.2%	87.8%
	H20 mg q.d	265	67.5%	85.3%
	OME 20 mg q.d.	251	64.9%%	84.9%
Proportion of Patients Healed by Age Group				
Age < 65 years	H40 mg q.d.	597	70.9%	87.8%
	H20 mg q.d	587	66.8%	83.1%
	OME 20 mg q.d.	574	62.0%	81.0%

Age ≥ 65 years	H40 mg q.d.	57	73.7%	86.0%
	H20 mg q.d	69	63.8%	89.9%
	OME 20 mg q.d.	76	56.6%	84.2%
Proportion of Patients Healed by Race				
Caucasian	H40 mg q.d.	591	70.9%	88.3%
	H20 mg q.d	595	65.5%	83.7%
	OME 20 mg q.d.	608	61.8%	82.1%
Black	H40 mg q.d.	49	77.6%	85.2%
	H20 mg q.d	43	83.7%	86.0%
	OME 20 mg q.d.	35	54.3%	71.4%
Proportion of Patients Healed by H. Pylori Status				
H. Pylori Positive	H40 mg q.d.	65	81.5%	89.2%
	H20 mg q.d	56	73.2%	85.7%
	OME 20 mg q.d.	68	66.2$	83.8%
H. Pylori negative	H40 mg q.d.	584	69.9%	87.3%
	H20 mg q.d	598	65.7%	83.6%
	OME 20 mg q.d.	51	60.0%	81.1%

Safety and Tolerability:

Serious Adverse Events – The distribution of serious adverse events is given below,

	SAEs	Discontinued from further treatment
H40 mg qd	6	4
H20 mg qd	8*	6
OME20 mg qd	6*	1
	20	11

* Patient 051/029 had 2 SAEs and died

** Including 4 cases of overdose.

Adverse Events – There is no meaningful difference in proportion of AE between the three treatment groups (43.3% in H40 mg, 44.7% in H20 mg and 41.0% in OME 20 mg). Most frequent adverse events were headache, abdominal pain, diarrhea, gastritis, nausea, and respiratory infection. There is no meaningful distribution difference among the three groups.

Reviewer's Comments

Clinical trial Study 172 is one of the two critical multicenter studies submitted by the sponsor of this NDA in support of the approval of "short-term treatment of erosive esophagitis associated with GERD". Study 172 consists of three treatment arms, H199/18 40 mg, H199/18 20 mg and OME 20 mg. The study was well planned, well conducted and well executed. Analyses results evaluated by reviewer were ITT population. But analyses based on PP population gave consistent results. The results of study 172 showed that H199/18 was effective after 4 weeks of treatment. The healing rate of H40 mg (71.1%) was higher than the OME 20 mg group (61.4%). But the dose-response relationship between H20 mg and H40 mg was not demonstrated.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between either H40 mg or H20 mg and OME20 mg.

II.B STUDY 173

Study 173 used a protocol similar to Study 712. It was a multicenter, randomized, double-blind, eight-week comparative efficacy and safety study of H199/18 40 mg and omeprazole 20 mg in subjects with erosive esophagitis.

The primary objective of the study is complete healing of erosive esophagitis of H40 mg q.d. and H20 mg q.d. compared to omeprazole 20 mg q.d. at week 8 of treatment.

The secondary objectives are

1. Efficacy, defined as complete healing of erosive esophagitis, of H40 mg q.d. compared to OME 20 mg at week 4 of treatment.
2. Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H40 mg q.d. as compared with OME 20 mg q.d. at week 4 and week 8 of treatment.
3. Time to resolution and relief of heartburn of H40 mg q.d, as compared to OME 2o mg q.d.
4. Safety and tolerability of H40 mg q.d., as compared to OME 20 mg q.d.

The study population consists of 1000 patients (adults 18 to 75 of age) with symptomatic erosive esophagitis (EE) enrolled at 75 centers in the U.S.

The sample size of 500 patients per treatment arm was calculated based on having 95% power to detect a 10% difference in complete healing rate of 85% for H 199/18 40 mg and 75% of OME 20 mg. The sample size calculated was performed using arcsine transformation, for a two-sided test, with Bonferroni correction for two comparisons (i.e. corrected type I error rate of 0.025).

Randomization was performed at each center.

The assessment of symptoms were similar to that of study 172.

Analysis Population: Patients participated could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event, or for other reasons unrelated to treatment. Distribution of randomization and disposition of patients entered into trial are given in the following Table II.B.1. The ITT population included all patients randomized to treatment, with no exclusion. In the PP population, patients excluded because of study exclusion criteria, compliance violations, prohibited concomitant medications, etc. The percentage of exclusion in PP population was 28.3% and was evenly distributed among the three treatment groups.

Table II.B.1 Distribution and Disposition of Patients Entered into Study 173

Screened N=1946			
Not Enrolled = 798			
	H 199/18 40 mg	OME 20mg	Total
Randomized (ITT Population)	576	572	1148
Week 4			
Completed	393	379	772
Ongoing	152	174	326
Discontinued	31	19	50
Week 8			
Completed	150	166	316
Discontinued	3	8	11
Safety Population (Rec'd at least 1 dose)	576	571	1147
PP Population	487	486	973
Patient Evaluability			
ITT Population	576	572	1148
Patients with Week 4 Endoscopy	552	556	1108
Patients with Week 8 Endoscopy	145	163	308
PP Population	487	486	973
Patients with Week 4 Endoscopy	487	486	973
Patients with Week 8 Endoscopy	131	146	277

Baseline measurements: The three treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – In ITT population, H40 mg q.d. group had a 1.9% higher healing proportion than OME 20 mg q.d. group at week 4 of treatment and 1.2% higher proportion at Week 8. The difference was not statistically significant (Table II.B.2).

Table II.B.2 EE Healing Proportion of the Treatment Groups in Study 173

Week	H40 mg	OME 20 mg	H40 mg vs OME 20 mg[a]	Stat Test
n	576	572		
4	393 (68.2%)	379 (66.3%)	1.9% N.S.	 CMH
8	501 (87.0%)	491 (85.8%)	1.2% N.S N.S. N.S.	 Log-rank Wilcoxon CMH

a: From sponsor's analysis with p-values adjusted for multiple comparisons (Hochberg).

The Secondary Efficacy Objectives:

Results of the secondary efficacy objectives were not reviewed because there were no statistical difference between H40 mg qd and OME 20 mg qd in the analysis of the primary efficacy objective.

Healing proportions in subgroups:

There was no meaningful difference among gender, race, age group and *H. Pylori* status and investigator site.

Reviewer's Comments
Clinical trial Study 173 was designed with a protocol similar to Study 172. It was well designed, conducted and executed. However, Study 173 failed to demonstrate the superiority of H40 mg qd over OME 20 mg qd as in Study 172. The difference found in this study was much moderate and statistically insignificant than Study 172.

Results of the safety analyses of this study demonstrated that H40 mg was generally safe and well tolerated.

II. C STUDY 222
Study 222 was designed to replicate the findings with H40 mg in Study 172. It was designed with a protocol very similar to Study 172. Only certain aspect of this study will be highlighted in this review.

The primary objective of the study is complete healing of erosive esophagitis of H40 mg q.d. compared to omeprazole 20 mg q.d. at Week 8 of treatment.

The secondary objectives are
1. Efficacy, defined as complete healing of erosive esophagitis, of H40 mg q.d. compared to OME 20 mg at week 4 of treatment.
2. Complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain by H40 mg q.d. as compared with OME 20 mg q.d. at Week 4 and Week 8 of treatment.
3. Time to resolution and relief of heartburn of H40 mg q.d, as compared to OME 2o mg q.d.
4. The safety and tolerability of H40 mg q.d., as compared to OME 20 mg q.d.

The study population consists of 1200 patients (adults 18 to 75 of age) with symptomatic erosive esophagitis (EE) enrolled at 163 centers in the U.S.

The sample size of 1040 patients per treatment arm was calculated based on having 95% power to detect a difference in complete healing rate of 93% of H 199/18 and 88% of OME 20 mg. The sample size calculated was performed using arcsine transformation, for a two-sided test, with Bonferroni correction for two comparisons (i.e. corrected type I error rate of 0.025).

Randomization was performed at each center.

The assessment of symptoms used the same schedule as of Study 172.

Analysis Population: Patients participated could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event, or for other reasons unrelated to treatment. Distribution of randomization and disposition

of patients entered into trial are given in the following Table II.C.1. The ITT population included all patients randomized to treatment, with no exclusion. In the PP population, patients excluded because of study exclusion criteria, compliance violations, prohibited concomitant medications, etc. The percentage of exclusion in PP population was 22.2% and was evenly distributed among the three treatment groups.

Table II.C.1 Distribution and Disposition of Patients Entered into Study 222

Screened N=4798, Not Enrolled = 2373			
	H 199/18 40 mg	OME 20mg	Total
Randomized (ITT Population)	1216	1209	2425
Week 4			
Completed	956	805	1761
Ongoing	217	364	581
Discontinued	43	40	83
Week 8			
Completed	173	173	310
Unhealed	72	177	249
Discontinued	8	14	22
Safety Population (Rec'd at least 1 dose)	1205	1200	2405
PP Population	1066	1066	2132
Patient Evaluability			
ITT Population	1216	1209	2425
Patients with Week 4 Endoscopy	1177	1180	2357
Patients with Week 8 Endoscopy	207	351	558
PP Population	1066	1066	2132
Patients with Week 4 Endoscopy	1066	1066	2132
Patients with Week 8 Endoscopy	185	325	510

Baseline measurements: The three treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – In ITT population, at Week 8, the complete healing proportions were 89.9% and 80.9% of patients treated with H40 mg q.d. and OME 20 mg q.d. respectively. The 9% difference was more than the targeted therapeutic gain of 5% at Week 8. The difference was statistically significant using log-rank, Wilcoxon or CMH test ($p<0.001$).

The secondary objectives -

1. H40 mg q.d. group had a 12.0% higher healing proportion than OME 20 mg q.d. group at week 4 of treatment. The difference was statistically significant with $p=0.001$ using CMH test.

Table II.C.2 EE Healing Proportion of the Treatment Groups in Study 222

Week	H40 mg	OME 20 mg	H40 mg vs OME 20 mg[a]	Stat Test
n	1216	1209		
4	956 (78.6%)	805 (66.6%)	12.0% 0.001	 CMH
8	1093 (89.9%)	978 (80.9%)	9.0% <0.001* <0.001* 0.001*	 Log-rank Wilcoxon CMH

a: From sponsor's analysis *: Statistically significant with multiple comparison adjustment (Hochberg).

2. Results of complete resolution and relief of GERD symptoms of heartburn, acid regurgitation, dysphagia, and epigastric pain at Week 4 are shown in Table II.C.3 and Table II.C.4. H40 mg groups had higher percentage in resolution and relief at Week than OME 20 mg group in all four GERD symptoms. However, the difference was statistically significant in heartburn ($p<0.001$ in resolution and $p=0.001$ for relief) and regurgitation ($p=0.003$ in resolution and $p=0.011$ in relief) only.

Table II.C.3 Proportion of Patients of Investigator-Recorded Complete Resolution of GERD Symptoms at Week 4

Treatment	N	Week 4	
		Proportion	p-value*
Heartburn			
H40 mg q.d.	1188	68.3%	<0.001
OME 20 mg q.d.	1183	58.1%	--
Regurgitation			
H40 mg q.d.	1188	80.1%	0.003
OME 20 mg q.d.	1182	75.2%	--
Dysphasia			
H40 mg q.d.	1188	92.1%	0.723
OME 20 mg q.d.	1182	91.2%	--
Epigastric Pain			
H40 mg q.d.	1188	83.5%	0.180
OME 20 mg q.d.	1182	81.8%	--

Modified from sponsor's Tables 14.2.13, Item 8, Vol 1

* CMH test, Compared with OMS 20 mg, p-value with no adjustment for multiple comparisons.

Table II.C.4 Proportion of Patients of Investigator-Recorded Relief of GERD Symptoms at Week 4

Treatment	N	Week 4	
		Proportion	p-value*
Heartburn			
H40 mg q.d.	1188	92.7%	0.001
OME 20 mg q.d.	1183	88.7%	--
Regurgitation			
H40 mg q.d.	1188	95.4%	0.011
OME 20 mg q.d.	1182	93.1%	--
Dysphasia			
H40 mg q.d.	1188	98.2%	0.808
OME 20 mg q.d.	1182	98.2%	--
Epigastric Pain			
H40 mg q.d.	1188	96.2%	0.472
OME 20 mg q.d.	1182	95.8	--

Modified from sponsor's Tables 14.2.15, Item 8, Vol 1

* CMH test, Compared with OMS 20 mg, p-value with no adjustment for multiple comparisons.

3. H40 mg group had a shorter time to first resolution, time to sustained resolution of heartburn than OME 20 mg group. The difference was statistically significant ($p<0.001$ log-rank test in both cases).

Healing of EE in subgroups:

There was no meaningful difference of proportion of patients healed between genders, races, ages and *H. Pylori* statuses.

Safety and Tolerability:

Serious Adverse Events – There was one death reported in the OME 20 mg group. distribution of serious adverse events is given below

	SAEs	Discontinued from further treatment
H40 mg qd	9	3
OME20 mg qd	7*	1
	16*	4

*: Sponsor indicated all 16 SAEs were not test medication related.

Adverse Events – There is no meaningful difference in proportion of AE between the two treatment groups (32.2% in H40 mg and 34.3% in OME 20 mg). Most frequent adverse events were headache, abdominal pain, diarrhea, gastritis, nausea, and respiratory infection. There is no meaningful distribution difference among the two groups. There is no difference between genders, age group (≥65 years age and <65 years age) or among the races.

Reviewer's Comments

Clinical trial Study 222 was submitted to replicate the results of Study 172 in efficacy of H40 mg in comparing to OME 20 mg. The study was well planned, well conducted and well executed. Analyses results evaluated by reviewer were ITT population. But analyses based on PP population gave consistent results. The results of study 222

showed that H199/18 was effective after 4 weeks of treatment. The healing rate at week 8 of H40 mg (93.7%) was higher than the OME 20 mg group (84.2%). The difference was statistically significant ($p<0.001$).

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between H40 mg and OME20 mg.

II. D STUDY 174

Study 174 was designed with a protocol very similar to Study 172 but with two arms H199/18 20mg qd and OME 20 mg qd. It was a randomized, double-blind, multicenter, parallel-group trial. It enrolled 1176 patients into 2 arms. The study's primary objective is complete healing of erosive esophagitis of H20 mg q.d. compared to omeprazole 20 mg q.d. at week 8 of treatment. The healing rate at Week 8 was 90.6% (95%CI =(88.1%, 93.0%)) for H20 mg and 88.3% (95%CI=(85.5%, 91.0%)) for OME 20 mg. The difference was not statistically significant using either log-rank or Wilcoxon test.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between H20 mg and OME20 mg.

II.E. REVIEWER'S SUMMARY OF CLINICAL TRIALS IN SUPPORT OF "SHORT-TERM (UP TO 8 WEEKS) TREATMENT OF EE ASSOCIATED WITH GERD"

The sponsor submitted 4 well-designed, conducted and executed multicenter clinical trials of this NDA in support of the approval of the ESOME Mg for the "short-term treatment of EE associated with GERD". All four studies were randomized, double-blind, parallel-arm clinical trials with treatment duration of 8 weeks. Study 172 compared the healing rate of H199/18 40 mg, H199/18 20 mg with OME 20 mg. Study 173 and Study 222 compared the healing rate of H199/18 40 mg with OME 20 mg. Study 174 compared the healing rate of H199/18 20 mg with OME 20 mg. The healing of EE was demonstrated by statistical superiority of H40 mg over OME 20 mg in Study 172 and 222. However, in Study 173, H40 mg was not differentiated from OME 20 mg. H20 mg was not differentiable from OME 20 mg in both Study 172 and Study 174. On the other hand, H40 mg was also not differentiated from H20 mg in Study 172. In addition, the superiority of H40 mg over OME 20 mg was demonstrated by comparing two treatments at different dose level and does not lead to the conclusion that H199/18 is superior to OME in healing EE.

There was no meaningful effect on the proportions of patients healed due to gender, race, or age group. There was no effect of *H. pylori* status at Week 8. There was difference observed at Week 4 in one clinical trial (Study 172).

In conclusion, the data support that H199/18 is active in healing of EE. The appropriate dose level to be recommended would rely on medical and pharmacodynamical interpretation of the data.

III. MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

III.A STUDY 177

Study 177 was a multicenter, randomized, double-blind, six-month comparative maintenance study to compare the efficacy, safety and tolerability of H199/18 20 mg, H199/18 40 mg and H199/18 10 mg with Placebo in healed erosive esophagitis subjects.

The primary objective of the study was, in patients with healed EE, to assess the maintenance of healing efficacy of H40 mg, H20 mg, and H10 mg in comparing to Placebo, at Month 6.

The secondary objectives were to assess changes in GERD symptoms by H40 mg, H20 mg and H10 mg, in comparing with Placebo.

The study population consists of 375 patients (adults 18 to 75 of age) with healed erosive esophagitis (EE) as verified on endoscopy at the completion of Study 172 and who were negative for *H. pylori* (by histology) at baseline of Study 172 at 71 investigator sites).

The sample size was determined to satisfy two criteria. One is to have 95% power to detect a 10% difference in maintenance of healing rate of 70% for H199/18 and 25% for Placebo with type I error rate of 0.0167 (a Bonferroni adjustment for 3 pairwise comparisons). It was calculated with arcsine transformation method that a sample size of 44 patients per treatment arm would be necessary.

Although the purpose of this study was not to compare the H199/18 doses to each other statistically, but the sponsor further enlarge the sample size in order to have sufficient "power" for the observed responses to identify a true dose response. For this purpose, it was assumed that the true response rates for two hypothetical dose groups (identified as H80% and H70%) were 70% and 80%. It was calculated that 75 patients per treatment was needed to assure a less than 10% probability that H70% would result in an observed response rate greater than that for H80%.

The sample size proposed (75 subjects per treatment group) was the greater of the two estimates.

Randomization Three hundred patients at 75 centers satisfied the inclusion/exclusion criteria. Patients were randomized to treatment in a 1:1:1:1 ratio (H40:H20:H10: Placebo).

Note that the test medication received in Study 172 was not blinded as a result of eligibility for this study. Each patient's medical history, P.E., blood and urine samples, and endoscopy results from the final visit in Study 172 were used as baseline values in the current study. The gastric biopsy results and histologic H pylori status at baseline of Study 172 were used as the baseline for Study 177.

Safety and efficacy measurements were assessed by the investigator on each subject at baseline, Month 1, Month 3 and Month 6. Details of the study flowchart of clinical and laboratory measurements are given in Table III.A.1.

If erosions (i.e. LA Classification Grade of A, B, C, or D) were seen at any visit, the patient was considered to have relapsed and was discontinued from the trial.

Table III.A.1 Study Flowchart of Clinical and Laboratory Measurements

Procedure	Baseline Day-1	Visit 1 Month 1	Visit 2 Month 3	Visit 3 Month 6
Informed Consent	x			
Medical History	x			
Physical Examination	x			x
Vital Signs	x	x	x	x
Laboratory Samples	x	x	x	x
Endoscopic Evaluation	x	x	x	x
Gastric Biopsy				x
Pregnancy Test	x			
Symptom Assessment	x	x	X	x
Concomitant Medication	x	x	x	x
Adverse Event Assessment		x	x	x
Dispense Study Drug	x	x	x	
Drug Accountability		x	x	x
End of Safety Status				x

Analysis Population: As summarized in Table A.III.2, a total of 191 patients (50.9%) completed this 6-month study. The percentage of completed patients decreased monotonically from H199/18 40 mg (72.8%) to Placebo (21.3%). The main reason for not completing the study was lack of therapeutic response (28%). A total of 35.2% patients had some protocol deviation. However, the groups were balanced with respect to PP deviation. The most frequent reason for exclusion from PP population was compliance violation (26.7%).

Table III.A.2 Distribution and Disposition of Patients Entered into Study 177

	H40	H20	H10	Placebo	Total
Number of Patients Planned and Analyzed					
Planned	75	75	75	75	300
Enrolled	92	98	91	94	375
Analyzed					
Efficacy: ITT	92	98	91	94	375
Pre-Protocol	77	88	79	70	314
Safety	92	98	91	92	373
Patient Disposition and EGD Evaluability					
ITT Population	92	98	91	94	375
Month 1 Endoscopy	81	81	74	75	331
Month 3 Endoscopy	72	80	61	29	342
Month 6 Endoscopy	67	62	49	21	199
PP Population	77	88	79	70	314
Month 1 Endoscopy	71	80	73	66	290
Month 3 Endoscopy	69	77	57	27	230
Month 6 Endoscopy	65	61	49	21	196

Reasons for not Completing the Study					
Not Complete	25	36	49	74	184
Lack of therapeutic Response	4	11	30	60	105
AEs	5	5	2	2	14
Sponsor/Individual Decision	7	4	6	5	22
Lost to Follow Up	5	10	7	2	24
Consent Withdrawn	4	6	4	5	19
Patients Excluded From PP Deviations					
Excluded from PP Population	30.8%	35.7%	30.8%	36.2%	35.2%
Entrance Violation at Baseline	9.8%	9.2%	6.6%	12.8%	9.6%
H Pylori at Baseline	3.3^	3.1%	1.1%	3.2%	2.7%
Compliance Violation	26.1%	26.5%	24.2%	29.8%	26.7%
Prohibited Concomitant Meds	7.6%	4.1%	3.3%	9.6%	6.1%
Others	9.8%	10.2%	8.8%	13.8%	10.7%

Baseline measurements: The four treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – In ITT population, all dropouts were considered failed to maintain healing of EE. The cumulative life-table rate of maintenance of healing of EE at Month 6 showed that each of the H199/18 treatment group (H40=87.9%, H20=78.7% and H10=54.2%) were higher than Placebo (29.1%). The differences were statistically significant ($p<0.001$ using either log-rank test or Wilcoxon test for H40, H20 and H10) with Hochberg's adjustment for multiple comparisons. The results of using PP population were consistent with ITT population (Table III.A.3). The maintenance rates observed in the three H199/18 dose levels suggested also a dose-response relationship.

Table III.A.3 Cumulative maintenance of EE Healing Rates by Month ITT Population, Study 177

Cumulative Statistic	H40 mg	H20 mg	H10 mg	Placebo
N	92	98	91	94
Month 1				
Crude Rate, n (%) **95% Crude CI**	86 (93.5%) (86.3%, 97.6%)	86 (87.8%) (81.3%, 94.3%)	70 (76.9%) (68.3%, 85.6%)	38 (40.4%) (30.5%, 50.4%)
Diff. from Placebo (P-value[a])	53.1% (0.001)	47.8% (0.001)	36.5% (0.001)	
Diff. from H10 (P-value[a])	16.6% (0.002)	10.9% (0.05)		
Diff. from H20 (P-value[a])	5.7% (>0.05)			
Life-table rate, % **95% CI**	97.8% (94.5%, 100%)	94.9% (90.5%, 99.3)	85.7% (78.5%, 92.9%)	54.3% (44.2%, 64.3%)
Diff. from Placebo (P-value[b])	43.5% (<0.001)	40.6% (<0.001)	31.4% (<0.001)	
Diff. from H10 (P-value[b])	12.1% (0.002)	9.2% (0.051)		
Diff. from H20 (P-value[b])	2.9% (>0.05)			

Month 3				
Crude Rate, n (%) **95% Crude CI**	73 (79.4%) (71.1%, 87.6%)	69 (70.4%) (61.4%, 79.5%)	50 (55.0%) (44.7%, 65.2%)	22 (23.4%) (1.8%, 64.3%)
Diff. from Placebo (P-value[a])	56.0% (0.001)	47.0% (0.001)	31.6% (0.001)	
Diff. from H10 (P-value[a])	24.4% (0.001)	15.4% (0.028)		
Diff. from H20 (P-value[a])	9.0% (>0.05)			
Life-table rate, % **95% CI**	96.5% (92.6%, 100%)	87.4% (80.4%, 94.4%)	67.2% (56.9%, 77.5%)	41.5% (30.2%, 52.8%)
Diff. from Placebo (P-value[b])	55.0% (<0.001)	45.9% (<0.001)	25.7% (<0.001)	
Diff. from H10 (P-value[b])	29.3% (<0.001)	20.2% (0.002)		
Diff. from H20 (P-value[b])	9.1% (>0.05)			
Month 6				
Crude Rate, n (%) **95% Crude CI**	61 (66.3%) (56.7%, 76.0%)	54 (55.1%) (45.3%, 65.0%)	37 (40.0%) (30.6%, 50.8%)	14 (14.9%) (7.7%, 22.1%)
Diff. from Placebo (P-value[a])	51.4% (0.001)	40.2% (0.001)	25.8% (0.001)	
Diff. from H10 (P-value[a])	25.6% (0.001)	14.4% (0.047)		
Diff. from H20 (P-value[a])	11.2% (>0.05)			
Life-table rate, % **95% CI**	87.9% (80.4%, 95.4%)	78.7% (69.5%, 87.8%)	54.2% (42.9%, 65.5%)	29.1% (17.6%, 40.6%)
Diff. from Placebo (P-value[c])	58.8% (<0.001)*	49.6% (<0.001)*	25.1% (<0.001)*	
Diff. from H10 (P-value[b])	33.7% (<0.001)	24.5% (0.026)		
Diff. From H20 (P-value[b])	9.2% (>0.05)			

From sponsor's Table 14.2.1, with modification and additions

a: Post hoc comparison using Chi-square test, no adjustment for multiple comparisons – reviewer's analysis

b: Post hoc comparison using Wilcoxon test, no adjustment for multiple comparisons – reviewer's analysis

c: Larger p-value of Log-rank test and Wilcoxon tests

* Statistically significant with Hochberg adjustment, sponsor's analysis.

The secondary objectives –

Recurred at Grade C of EE – As shown in Table III.A.4, the mean time to recurrence decreases with the dose of H199/18. H40 has no patients had a recurrence. The proportion of recurrence was greatest in Placebo group. The difference in recurrence proportion was statistically significant in H40 mg and H20 mg groups comparing to the Placebo group.

Heartburn – At Month 1, heartburn and other GERD symptoms, namely regurgitation, dysphasia and epigastric pain were absent in the majority of H199/18 patients but present in most patients receiving Placebo. The difference was statistically significant between any dose of H199/18 and Placebo treatment. The difference between high and low dose of H199/18 groups was inconsistent in terms of dose-response relationship and statistical significance p-value based on reviewer's post hoc Chi-square tests.

Table III.A.4 Summary of Results of Analysis for Secondary Objectives
ITT Population, Study 177

Cumulative Statistic	H40 mg	H20 mg	H10 mg	Placebo
N	92	98	91	94
Mean Time to Recurred at Grade C (Days)	130	101	80	46
Proportion of Patients Who Recurred at Grade C	0%	11.8%	2.8%	16.1%
Diff. from Placebo (P-value[a])	16.1% (0.001)	4.1% (>0.05)	13.3% (0.001)	
Diff. from H10 (P-value[a])	11.8% (0.001)	--		
Diff. from H20 (P-value[a])	-2.8% (>0.05)			

Heartburn Month 1				
Proportion of Patients Who Were Heartburn Free	71.3%	63.7%	50.6%	15.5%
Diff. from Placebo (P-value[b])	55.8%(p=0.001)	48.2% (0.001)	35.1% (0.001)	
Diff. from H10 (P-value[a])	20.7% (0.005)	--		
Diff. from H20 (P-value[a])	7.6% >0.05)			
Regurgitation Month 1				
Proportion of Patients Who Were Regurgitation Free	80.5%	73.6%	65.1%	27.4%
Diff. from Placebo (P-value[b])	53.1%(p=0.001)	46.2% (0.001)	37.7% (0.001)	
Diff. from H10 (P-value[a])	15.4% (0.018)	--		
Diff. from H20 (P-value[a])	6.9% (>0.05)			
Dysphasia Month 1				
Proportion of Patients Who Were Dysphasia Free	94.3%	92.3%	97.6%	81.0%
Diff. from Placebo (P-value[b])	13.3%(p=0.010)	11.3% (0.026)	16.6% (0.001)	
Diff. from H10 (P-value[a])	-3.3% (>0.05)	--		
Diff. from H20 (P-value[a])	2.0% (>0.05)			
Epigastric Pain Month 1				
Proportion of Patients Who Were Epigastric Pain Free	77.0%	84.6%	80.7%	45.2%
Diff. from Placebo (P-value[b])	31.8%(p=0.001)	39.4% (0.001)	35.5% (0.001)	
Diff. from H10 (P-value[a])	-3.3% (>0.05)	--		
Diff. from H20 (P-value[a])	7.6% (>0.05)			

From sponsor's Table 14.2.13-4.2.15, with modification and additions
a:Post hoc analysis without baseline adjustment, Chi-square test - Reviewer's analysis
b: Cochran-Mantel Haenszel test Stratified by baseline – Sponsor's analysis

Effects in Subgroups:
Proportion of maintenance of EE status was tabulated at Month 6 for the subgroups of GELUSIL use, gender, race, age group, and LA classification grade by sponsor. There was no meaningful difference to indicate the subgroup effect.

Safety and Tolerability:
Exposure length - There is large exposure time difference between the three test treatments and placebo. There were more than 80% of patients in each test treatment group in the study at Week 4 in comparing to slightly more than one-half of patients receiving Placebo treatment. By 18 weeks (4 months), only 21.7% of Placebo patients and 48.4% of H10 patients remained in the study. In contrast, 64.3% of H20 patients and 71.7% of H40 patients remained in the study at this time. The mean lengths of treatment of the 4 treatment groups were 146 days of H40, 137 days of H20, 116 days of H10 patients, comparing to only 61,5 days of Placebo patients.

Serious Adverse Events – The distribution of serious adverse events is given below. All SAEs were considered by the investigator to be unlikely related to the test medication.

	SAEs
H40 mg qd	2
H20 mg qd	4
H10 mg qd	1
Placebo qd	0
Total	7

Adverse Events – There is no meaningful difference in distribution of AE between the four three test treatment groups and Placebo group. Most frequent adverse events were headache, abdominal pain, diarrhea, nausea, flatulence and respiratory infection

Reviewer's Comments
Clinical trial Study 177 is one of the two critical multicenter studies submitted by the sponsor of this NDA in support of the approval of orally administrated NEXIUM in the "prevention of relapse and maintenance of symptom resolution of erosive esophagitis". The study was a multicenter, randomized, 4 parallel arms, double-blind, placebo-controlled, 6-month study designed to evaluate the efficacy and safety of 3 dose level of H199/18 vs Placebo inpatients with healed EE. The study was well designed, well conducted and well executed. The primary objective of the study to assess the proportion of patients maintained complete healing of EE on esophago-gastro-duodenoscopy (EGD) assessment at Month 1, 3 and 6 of treatment. The secondary objective was to assess the proportion of patients with the presence of GERD symptoms including heartburn, regurgitation, dysphasia and epigastric pain at Month 1, Month 3 and Month 6.

Results of the study support the claim of orally administrated H188/19 maintaining the resolution of symptoms of EE and healed patients. The rate of healing was statistically significantly greater in each H199/18 group than the Placebo group (p-value <0.001 using either log-rank test or Wilcoxon test). It was evident that the rate of maintenance of healing increased with the dose of H199/18 but the efficacy difference between H40 and H20 was too small to be of any significance. It was shown in reviewer's post hoc analyses (Table III.A.3 and III.A.4) comparing H40 and H20 that there was no statistically significant difference between the two doses with any of the primary or secondary variables at any time. In contrast, the there were more significant difference in maintenance of healing between H20 and H10 at most of the times (Table III.A.3).

There was no death, no drug-related SAEs and no unexpected clinically meaningful changes in routine laboratory parameters or vital signs.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between H40 mg and OME20 mg.

III.B STUDY 178
Study 178 was a multicenter, randomized, double-blind, six-month comparative maintenance study to compare the efficacy, safety and tolerability of H199/18 20 mg, H199/18 40 mg and H199/18 10 mg with Placebo in healed erosive esophagitis subjects. It has the exactly the same design, randomization scheme, blinding, objectives, study population, sample size determination and schedule of evaluations as Study 177.

Analysis Population: As summarized in Table III.B.1, a total of 187 patients (58.8%) completed this 6-month study, completion rates were highest in H40 (75.6%) and H20 (84.1%) groups. The lowest rate was in Placebo (16.9%). The main reason for not completing the study was lack of therapeutic response (24.5%). A total of 32.1% patients

had some protocol deviation. However, the groups were balanced with respect to PP deviation. The most frequent reason for exclusion from PP population was compliance violation (21.1%). These results were in general consistent with Study 177.

Table III.B.1 Distribution and Disposition of Patients Entered into Study 178

	H40	H20	H10	Placebo	Total
Number of Patients Planned and Analyzed					
Planned	75	75	75	75	300
Enrolled	82	82	77	77	318
Analyzed					
Efficacy: ITT	82	82	77	77	318
Per-Protocol	66	73	65	61	265
Safety	81	81	76	77	315
Patient Disposition and EGD Evaluability					
ITT Population	82	82	77	77	318
Month 1 Endoscopy	70	72	65	65	272
Month 3 Endoscopy	67	74	51	23	215
Month 6 Endoscopy	64	69	46	13	192
PP Population	66	73	65	61	265
Month 1 Endoscopy	63	67	59	57	246
Month 3 Endoscopy	62	70	47	19	198
Month 6 Endoscopy	60	66	46	12	184
Reasons for not Completing the Study					
Not Complete	20	13	34	64	131
Lack of therapeutic Response	2	5	23	48	78
Aes	3	3	0	2	8
Sponsor/Individual Decision	3	0	4	4	11
Lost to Follow Up	9	2	4	1	16
Consent Withdrawn	3	3	3	9	18
Patients Excluded From PP Deviations					
Excluded from PP Population	36.6%	25.6%	31.2%	35.1%	32.1%
Entrance Violation at Baseline	15,9%	13.4%	15.6%	10.4%	13.8%
H Pylori at Baseline	2.4%	0.0%	1.3%	3.9%	1.9%
Compliance Violation	23.2%	14.6%	19.5%	27.3%	21.1%
Prohibited Concomitant Meds	2.4%	2.4%	5.2%	6.5%	4.1%
Others	15.9%	3.7%	5.2%	7.8%	8.2%

Baseline measurements: The treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – In ITT population, the cumulative life-table rate of maintenance of healing of EE at Month 6 showed that each of the H199/18 treatment group (H40=93.6%, H20=93.2% and H10=57.1%) were higher than Placebo (29.0%). The differences were statistically significant ($p<0.001$ using either log-rank test or Wilcoxon test for H40, H20 and H10) with Hochberg's adjustment for multiple comparisons. The results of using PP population were consistent with ITT population (Table III.B.2). The maintenance rates observed in the three H199/18 dose levels suggested also a dose response relationship.

Table III.B.2 Cumulative maintenance of EE Healing Rates by Month ITT Population, Study 178

Cumulative Statistic	H40 mg	H20 mg	H10 mg	Placebo
N	82	82	77	77
Month 1				
Crude Rate, n (%) 95% Crude CI	73 (89.0%) (80.1%, 94.9%)	80 (97.6%) (91.4%, 99.8%)	56 (72.7%) (62.8%, 82.7%)	27 (35.1%) (24.4%, 45.7%)
Diff. From Placebo (P-value[a])	53.9% (<0.001)	62.5% (<0.001)	37.6% (0.001)	
Diff. From H10 (P-value[a])	6.3% (0.009)	24.9% (0.001)		
Diff. From H20 (P-value[a])	-8.6% (0.029)			
Life-table rate, % 95% CI	100% --	100% --	77.9% (68.7%, 87.2%)	42.5% (31.8%, 53.9%)
Diff. From Placebo (P-value[b])	57.1% (<0.001)	57.1% (<0.001)	35.0% (<0.001)	
Diff. From H10 (P-value[b])	22.1% (0.001)	22.1% (<0.001)		
Diff. From H20 (P-value[b])	0.0% (>0.05)			
Month 3				
Crude Rate, n (%) 95% Crude CI	69 (84.1%) (76.3%, 92.0%)	71 (86.6%) (77.2%, 93.2%)	49 (63.6%) (52.9%, 74.4%)	14 (18.2%) (9.6%, 26.8%)
Diff. From Placebo (P-value[a])	65.9% (<0.001)	68.4% (<0.001)	45.4% (<0.001)	
Diff. From H10 (P-value[a])	20.5% (0.003)	23.0% (0.001)		
Diff. From H20 (P-value[a])	-2.5% (>0.05)			
Life-table rate, % 95% CI	98.6% (95.8%, 100%)	96.0% (91.4%, 100%)	72.0% (61.8%, 82.2%)	29.0% (17.7%, 40.3%)
Diff. From Placebo (P-value[b])	69.6% (<0.001)	67.0% (<0.001)	43.0% (<0.001)	
Diff. From H10 (P-value[b])	26.6% (0.001)	24.0% (<0.001)		
Diff. From H20 (P-value[b])	2.6% (>0.05)			
Month 6				
Crude Rate, n (%) 95% Crude CI	56 (68.3%) (58.2%, 78.4%)	67 (81.7%) (73.3%, 90.1%)	34 (44.2%) (33.1%, 55.2%)	12 (15.6%) (7.4%, 23.7%)
Diff. From Placebo (P-value[a])	52.7% (<0.001)	66.1% (<0.001)	28.6% (0.001)	
Diff. From H10 (P-value[a])	24.1% (0.002)	37.5% (0.001)		
Diff. From H20 (P-value[a])	-13.4% (>0.05)			
Life-table rate, % 95% CI	93.6% (87.4%, 99.7%)	93.2% (87.4%, 99.0%)	57.1% (45.2%, 69.0%)	29.0% (17.7%, 40.3%)
Diff. From Placebo (P-value[c])	64.6% (<0.001)*	64.2% (<0.001)*	28.1% (<0.001)*	
Diff. From H10 (P-value[b])	36.5% (<0.001)	36.1% (<0.001)		
Diff. From H20 (P-value[b])	0.4% (>0.05)			

From sponsor's Table 14.2.1, with modification and additions

a: Post hoc comparison using Chi-square test, no adjustment for multiple comparisons – reviewer's analysis

b: Post hoc comparison using Wilcoxon test, no adjustment for multiple comparisons – reviewer's analysis

c: The larger p-value of Log-rank test and Wilcoxon tests - sponsor's analysis.

*: significant with Hochberg adjustment- sponsor's analysis.

The secondary objectives –

Recurred at Grade C of EE – As shown in Table III.B.3, the mean time to recurrence decreases with the dose of H199/18. H40 had no patient that had a recurrence. The proportion of recurrence was greatest in H20 (20.0%) and the placebo group (17.7%).

Heartburn – At Month 1, heartburn and other GERD symptoms, namely regurgitation, dysphasia and epigastric pain were absent in the majority of H199/18 patients but present in most patients receiving Placebo. The difference was statistically significant between any dose of H199/18 and Placebo treatment. The difference between high and low dose of H199/18 groups was inconsistent in terms of dose-response relationship and statistical significance p-value based on reviewer's post hoc Chi-square tests.

Table III.B.3 Summary of Results of Analysis for Secondary Objectives
ITT Population, Study 178

Cumulative Statistic	H40 mg	H20 mg	H10 mg	Placebo
N	75	80	74	73
Mean Time to Recurred at Grade C (Days)	163	115	75	33
Proportion of Patients Who Recurred at Grade C	0%	20.0%	10.0%	17.7%
Heartburn Month 1				
Proportion of Patients Who Were Heartburn Free	78.7%	61.3%	51.4%	17.8%
Diff. from Placebo P-value[b]	<.001	<0.001	<0.001	
Diff. from H10 P-value[a]	<.001	>0.05		
Diff. from H20 P-value[a]	0.023			
Regurgitation Month 1				
Proportion of Patients Who Were Regurgitation Free	77.3%	73.8%	60.8%	34.2%
Diff. from Placebo P-value[b]	<0.001	<0.001	<0.001	
Diff. from H10 P-value[a]	0.036	>0.05		
Diff. from H20 P-value[a]	>0.05			
Dysphasia Month 1				
Proportion of Patients Who Were Dysphasia Free	93.3%	92.5%	85.1%	76.7%
Diff. from Placebo P-value[b]	0.012	0.005	>0.05	
Diff. from H10 P-value[a]	>0.05	>0.05		
Diff. from H20 P-value[a]	>0.05			
Epigastric Pain Month 1				
Proportion of Patients Who Were Epigastric Pain Free	84.0%	77.5%	68.9%	56.2%
Diff. from Placebo P-value[b]	<0.001	0.004	>0.05	
Diff. from H10 (P-value[a])	0.022	>0.05		
Diff. from H20 (P-value[a])	>0.05			

From sponsor's Table 14.2.13-4.2.15, with modification and additions
a:Post hoc analysis without baseline adjustment, Chi-square test - Reviewer's analysis
b: Cochran-Mantel Haenszel test Stratified by baseline – Sponsor's analysis

Subgroup effects:
Male patients appeared to have a lower rate of maintenance of healing of EE and a higher rate of recurrence than female. There did not appear to be any relationship of GELUSIL use to H199/18 dose or duration in the trial of the H199/18 treatment groups. There was no meaningful effect on maintenance due to other subgroup factors such as race, age group, LA classification, severity at baseline of Study 172.

Safety and Tolerability:
Exposure length - There is large exposure time difference between the three test treatments and placebo. There were more than 88% of patients in each test treatment group in the study at Week 4 in comparing to 70% of patients receiving Placebo treatment. By 18 weeks (4 months), only 16.9% of Placebo patients and 57.9% of H10 patients remained in the study. In contrast, 76.5% of H20 patients and 85.2% of H40 patients remained in the study at this time. The mean lengths of treatment of the 3 H199/18 groups ranged from 120 days to 161 days. In contrast, the mean length of the Placebo group was 59 days.

Serious Adverse Events – The distribution of serious adverse events is given below. All SAEs were considered by the investigator to be unlikely related to the test medication.

	SAEs
H40 mg qd	2
H20 mg qd	4
H10 mg qd	1
Placebo qd	0
Total	7

Adverse Events – There is no meaningful difference in distribution of AE between the four three test treatment groups and Placebo group. Most frequent adverse events were headache, abdominal pain, diarrhea, nausea, flatulence and respiratory infection

Reviewer's Comments

Clinical trial Study 178 is the other critical multicenter studies submitted by the sponsor of this NDA in support of the approval of orally administrated NEXIUM in the "prevention of relapse and maintenance of symptom resolution of erosive esophagitis". The study was a multicenter, randomized, 4 parallel arms, double-blind, placebo-controlled, 6-month study designed to evaluate the efficacy and safety of 3 dose levels of H199/18 vs Placebo inpatients with healed EE. The study was well designed, well conducted and well executed. The primary objective of the study to assess the proportion of patients maintained complete healing of EE on esophago-gastro-duodenoscopy (EGD) assessment at Month 1, 3 and 6 of treatment. The secondary objective was to assess the proportion of patients with the presence of GERD symptoms including heartburn, regurgitation, dysphasia and epigastric pain at Month 1, Month 3 and Month 6.

Results of the study support the claim of orally administrated H188/19 maintaining the resolution of symptoms of EE and healed patients. The rate of healing was statistically significantly greater in each H199/18 group than the Placebo group (p-value <0.001 using either log-rank test or Wilcoxon test). At Month 6, the cumulative life-table rate of maintaining healing of EE of the three H199/18 test treatment groups were

Cumulative Life-Table Rate of Maintenance Healing of EE, and 95% CI	
H40	93.6% (87.4%, 99.7%)
H20	93.2% (87.4%, 99.0%)
H10	57.1% (45.2%, 69.0%)

It was evident that the rate of maintenance of healing increased with the dose of H199/18 but the efficacy difference between H40 and H20 was too small to be of any significance. It was shown in reviewer's post hoc analyses (Table III.B.2 and III.B.3) comparing H40 and H20 that there was no statistically significant difference between the two doses with any of the primary or secondary variables at any time. In contrast, there were more significant difference in maintenance of healing between H20 and H10 at most of the times (Table III.B.2).

In general, H199/18 was safe and well tolerated as treatment to maintain the healed EE. There was no death, no drug-related SAEs and no unexpected clinically meaningful changes in routine laboratory parameters or vital signs.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between H40 mg and OME20 mg.

III.C. REVIEWER'S SUMMARY OF CLINICAL TRIALS IN SUPPORT OF MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

The sponsor submitted two well designed, well conducted and well executed multiple center randomized, double blind clinical trials to support the usage of H199/18 in maintaining healing of EE of patients with healed EE. The results of these two studies with the identical design demonstrated that H199/18 is effective and safe for the proposed indication. In addition, the evidences of the two studies indicate that H20 is as safe and effective as H40, the recommended dose by the sponsor.

There did not appear to be any relationship of GELUSIL use to H199/18 dose or duration in the trials of the H199/18 treatment groups. There was no meaningful effect on maintenance due to other subgroup factors such as race, age group, LA classification, severity at baseline. Male patients appeared to have a lower rate of maintenance of healing of EE and a higher rate of recurrence than female in Study 178. But it was not replicated in Study 177.

IV. TREATMENT OF SYMPTOMATIC GERD

IV.A STUDY 225

Study 225 was a multicenter, randomized, double-blind, eight-week comparative efficacy and safety study of H199/18 20 mg, H199/18 40 mg and Placebo in subjects with symptomatic GERD.

The primary objective of the study was complete resolution of heartburn (HB) per diary card, of 4 weeks of treatment of H199/18 40mg qd and H199/18 20 mg qd compared to Placebo in subjects with symptomatic gastro-esophageal reflux disease (s-GERD).

The secondary objectives were

1. Efficacy, defined as complete resolution of heartburn per diary card, of H40 mg qd and H20 mg qd, compared to Placebo qd at weeks 1,2, and 4.of treatment. In this objective, '4 weeks' was restricted to the data from the subset of subjects with data at Week 4.
2. Efficacy, defined as relief of HB per diary card, of H40 mg qd and H20 mg compared with Placebo qd at each of Weeks 1,2 and 4.
3. Efficacy, as defined by the percentage of days without HB per diary card, of H40 mg qd and H20 mg qd compared with Placebo qd at each of Weeks 1, 2 and 4.

4. Efficacy, as defined by the percentage of days without nocturnal HB per diary card, of H40 mg qd and H20 mg qd compared with Placebo qd at each of Weeks 1, 2 and 4.
5. Efficacy, as defined by time to first resolution of HB and time to first resolution of nocturnal HB per diary card, of H40 mg qd and H20 mg qd compared with Placebo qd.
6. Efficacy, as defined by resolution of HB, acid regurgitation, dysphasia, and epigastric pain symptoms per investigator assessment of H40 mg qd and H20 mg qd compared with Placebo qd at each of Weeks 1, 2 and 4.
7. Efficacy, as defined as a measure by the overall treatment evaluation (OTE), of H40 mg qd and H20 mg qd compared with Placebo qd at each of Weeks 1, 2 and 4.
8. Safety and tolerability of H20 mg qd. and H40 mg qd, as compared to Placebo qd.

The study population consists of 368 patients (from a total of 1021 screened) with s-GERD at 26 centers in the U.S. The inclusion/exclusion criteria were adequate for the type of study.

The sample size of 100 patients per treatment arm was calculated based on having 95% power to detect a difference in complete healing rate of 60% for each dose of H 199/18 and 30% of Placebo. The sample size calculated was performed using arcsine transformation, for a two-sided test, with Bonferroni correction for two comparisons (i.e. corrected type I error rate of 0.025).

Randomization was performed at each center.

The assessment of symptoms was completed by the investigator on each subject at baseline, Week 2 and 4. The GERD symptoms of heartburn (HB), acid regurgitation, dysphagia, and epigastric pain were assessed for the 7 days prior to the visit. Details of the study flowchart of clinical and laboratory measurements are given in Table IV.A.1.

Table IV.A.1 Study Flowchart of Clinical and Laboratory Measurements

Procedure	Baseline	Week 2	Week 4
	Day-7 to -1	Day 14 ±2days	Day 28±4 days
Informed Consent	x		
Medical History	x		
Physical Examination	x		x
Vital Signs	x	x	x
Laboratory Samples	x		x
Diary Card Review		x	x
EGD	x	x	x
Gastric Biopsy	x		
Pregnancy Test	x		
Dispense Diary Card	x		
GERD Symptom Assessment	x	x	x
Adverse Event Assessment		x	x
Review Concomitant Medications	x	x	x
Dispense Study Drug	x	x	
Drug Accountability		x	x

Analysis Population: Patients participated could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event, or for other reasons unrelated to treatment. Distribution of randomization and disposition of patients entered into trial are given in the following Table IV.A.2. The ITT population included all patients randomized to treatment, with no exclusion. In the PP population, patients excluded because of study exclusion criteria, compliance violations, prohibited concomitant medications, etc. The percentage of exclusion in PP population was 6% and was evenly distributed among the three treatment groups.

Table IV.A.2 Distribution and Disposition of Patients Entered into Study 225

Screened N=1021				
Not Enrolled = 653				
	H 199/18 40 mg	H199/18 20 mg	OME 20mg	Total
Randomized (ITT Population)	123	121	124	368
Completed	114	113	117	334
Not Completed	9	8	7	24
Adverse Event	2	1	0	3
Sponsor/Investigator Decision	2	0	2	4
Lost to Follow-Up	1	0	2	3
Consent Withdraw	3	3	3	9
Lack of Therapeutic Response	1	4	0	5
Safety Population (Rec'd at least 1 dose)	122	120	123	366
PP Population	115	117	114	346
Excluded from PP Population	8	4	10	22
Medical History	1	1	5	7
PPI Use Prior to Baseline Visit	0	1	0	2
H2-Receptor Use Prior to Baseline EGD	1	0	0	1
Concomitant Pro-motility Drugs	0	0	2	2
Study Dug Compliance	6	2	2	10
Other Reasons	0	0	1	1

Baseline measurements: The three treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – The proportion of patients with complete resolution reporting no heartburn by the end of trial was 33.3%, 33.9% and 13.7% for treatment with H40, H20 and Placebo respectively in ITT population. There was a statistically significant difference between H40 and Placebo ($p<0.001$), as well as between H20 and Placebo ($p<0.001$) (Table IV.A.3). The therapeutic gain about 20% in each of the H199/18 treatment groups over Placebo group was less than the targeted efficacy of 30%. The results of PP population were consistent with ITT population. There was no statistically significant difference between H40 group and H20 group.

Table IV. A.3[a] Complete Resolution of Heartburn As Recorded on the Diary Card, ITT Population, Study 225

	H40 mg qd	H20 mg qd	Placebo qd
Primary Objective (Reports at Final Visit)			
N	123	117	114
Complete Resolution of HB n (%) **95% CI**	41 (33.3%) (25.0%, 41.7%)	41 (33.9%) (25.5%, 42.3%)	17 (13.7%) (7.7%, 19.8%)
Chi-Square test p-value vs. Placebo	<0.001*	0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		
Secondary Objective #1			
Week 1			
N	119	120	123
Complete Resolution of HB n (%) **95% CI**	24 (20.2%) (13.0%, 27.4%)	12 (10.0%) (4.6%, 15.4%)	3 (2.4%) (0.0%, 5.2%)
Chi-Square test p-value vs. Placebo	<0.001*	0.014*	
Chi-Square test p-value vs. H20 mg	>0.028[b]		
Week 2			
N	119	119	122
Complete Resolution of HB n (%) **95% CI**	31 (26.1%) (18.2%, 33.9%)	30 (25.2%) (17.4%, 33.0%)	11 (9.0%) (3.9%, 14.1%)
Chi-Square test p-value vs. Placebo	<0.001*	0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		
Week 4			
N	115	110	117
Complete Resolution of HB n (%) **95% CI**	39 (33.9%) (25.3%, 42.6%)	36 (32.7%) (24.0%, 41.5%)	17 (14.5%) (8.1%, 20.9%)
Chi-Square test p-value vs. Placebo	0.001*	0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		

a: Sponsor's Table 14.2.3 with modification

*: Statistically significant with p-value < 0.025 of chi-square test for primary objective; and with p-value<0.05 of chi-square test with secondary objectives. It is a correction to the sponsor's legend.

b: Reviewer's Post Hoc Analysis.

The secondary objectives –

1. The proportion of patients that reported complete resolution of HB increased over time in all three treatment groups. At each time point there was a dose-response relationship suggested by the data. At each time point, the resolution proportion of both H199/18 treatment groups were significantly higher than the placebo group with the largest p-value being <0.014 (Table IV.A.3). However, there were no statistically significant difference between H40 and H20 group except at Week 1 (p=0.0258 with no adjustment).
2. Proportion of relief of HB per diary card increased with time in all treatment groups. The proportions of H40 mg qd and H20 mg qd were greater than Placebo qd group at each of Weeks 1,2 and 4 and at final visit. The difference was all statistically significant using chi-square test (Table IV.A.4).

Table IV. A.4[a] Relief of Heartburn As Recorded on the Diary Card, ITT Population, Study 225

	H40 mg qd	H20 mg qd	Placebo qd
Week 1			
N	119	120	123
Relief of HB n (%) **95% CI**	32 (26.9%) (18.9%, 34.9%)	21 (17.5%) (10.7%, 24.3%)	4 (3.3%) (0.1%, 6.4%)
chi-square test p-value vs. Placebo	<0.001*	0.001*	
Week 2			
N	118	119	122
Relief of HB n (%) **95% CI**	42 (35.3%) (26.7%, 43.9%)	41 (34.5%) (25.9%, 43.0%)	20 (16.5%) (9.9%, 23.1%)
chi-square test p-value vs. Placebo	0.001*	0.001*	
Week 4			
N	115	112	117
Relief of HB n (%) **95% CI**	57 (50.0%) (40.8%, 59.2%)	46 (41.8%) (32.6%, 51.0%)	32 (27.4%) (19.3%, 35.4%)
chi-square test p-value vs. Placebo	<0.001*	0.022*	
Final Visit			
N	115	112	117
Complete Resolution of HB n (%) **95% CI**	56 (45.5%) (36.7%, 54.3%)	53 (43.8%) (35.0%, 52.6%)	32 (25.8%) (18.1%, 33.5%)
chi-square test p-value vs. Placebo	0.001*	0.001*	

a: Sponsor's Table 14.2.4 with modification
*: Statistically significant with p-value < 0.05 of chi-square test.

3. The percentage of days without HB per diary card increased with time in all three treatment groups. The mean percentages of H40 mg qd and H20 mg qd groups were higher than the Placebo qd group at each of Weeks 1, 2 and 4. The differences were all statistically significant (Table IV.A.5).

Table IV. A.5[a] Percentage of Heartburn-Free Days As Recorded on the Diary Card, ITT Population, Study 225

	H40 mg qd	H20 mg qd	Placebo qd
Week 1			
N	119	120	123
Mean (SD)	47.3 (38.9)	41.9 (33.0)	24.6 (27.6)
p-Value vs Placebo ANOVA	<0.001*	<0.001*	
Week 2			
N	118	119	122
Mean (SD)	53.6 (39.7)	55.3 (37.9)	37.2 (35.1)
p-Value vs Placebo ANOVA	0.001*	0.001*	
Week 4			
N	115	112	117
Mean (SD)	62.8 (38.7)	62.7 (37.1)	46.4 (35.8)
ANOVA p-Value, compared to Placebo	0.001*	0.001*	

a: Sponsor's Table 14.2.6 with modification
*: Statistically significant with p-value < 0.05.

4. The mean severity of HB were lower of the two H199/18 groups in comparison to the Placebo group at Week 1, 2, 4 and at the final visit. The differences were all statistically significant at 0.05 level using two-way ANOVA.
5. The percentage of heartburn-free nights was greater in H40 mg and H20 mg groups than the Placebo group at Week 1, 2 and 4. The differences were all statistically significant using ANOVA.

6. The time to first resolution of HB was shorter in H40 and H20 group than the Placebo group. Both differences were statistically significant using Log-rank test. The time to first nocturnal heartburn was also shorter in H40 mg and H20 mg groups than the Placebo group. However, the differences were not statistically significant.
7. Results of investigator-assessed resolution of heartburn and acid regurgitation at Week 2 and Week 4 were all improved for H40 and H20 over the Placebo group. All the differences were statistically significant using Cochran-Mantel-Haenszel test stratified by baseline rating of the symptoms.
8. Results of investigator-assessed resolution of dysphasia and epigastric pain at Week 2 and Week 4 were not significantly better for either H40 or H20 over Placebo.
9. Each patient's assessment of overall treatment evaluation (OTE) were combined into a 15 point scale (ranging from "A very great deal worse" to "About the same" to " A great deal better") were analyzed. The distributions of OTE based on the 15 point scale of H40 mg and H 20 mg were compared with Placebo using a Wilcoxon rank sum test. Both H40 mg and H20 groups ranked OTE showed a significantly higher preference than the Placebo group with $p<0.001$ at Week 2 as well as Week 4.

Primary Efficacy by Subgroups

Relative treatment effects were similar for each gender, although male patients appeared to respond more favorably to the H40 and PL treatments. There was a lower response rate observed in patients < 65 years of age than the older age group. Given the small number of patients of 65 years of age or more (n=12 of H40 ; n=17 of H20; n=8 of Placebo), the difference was not statistically meaningful. There was no noticeable difference between Caucasian and Black patients.

The presence of H. pylori at baseline appeared to improve the chance of complete resolution of HB in all three treatment groups (Table IV.A.6).

Table IV.A.6 Proportion of Patients with Complete Resolution of Heartburn at Final Visit by *H. pylori* Status at Baseline

Resolution of HB	H40 [n=123]	H20 [n=121]	Placebo [n=124]
***H. pylori* Negative Patients**			
N	84	82	94
Resolved	23 (27.4%)	26 (31.7%)	8 (8.5%)
Not Resolved	61 (72.6%)	56 (68.3%)	86 (91.5%)
***H. pylori* Positive Patients**			
N	39	37	29
Resolved	18 (46.2%)	15 (40.5%)	8 (27.6%)
Not Resolved	21 (53.8%)	22 (59.5%)	21 (72.4%)

Safety and Tolerability:

Serious Adverse Events – There was only one patient in Placebo group had a serious adverse event that was unlikely related to medication by investigator's assessment.

Adverse Events – There was no meaningful difference in proportion of AE between the three treatment groups (35% to 41% of patients had at least one AE in each group). Most frequent adverse events were headache, abdominal pain, diarrhea, gastritis and nausea. There was no meaningful distribution difference among the three groups.

Reviewer's Comments
Clinical trial Study 225 is one of the two critical multicenter studies submitted by the sponsor of this NDA in support of the approval of "treatment of symptomatic gastroesophageal reflux disease (s-GERD)". According to the sponsor, the recommended dose is 20 mg once daily for 4 weeks. Study 225 randomized 368 patients into treatment arms, H199/18 40 mg, H199/18 20 mg and Placebo. The study was well planned, well conducted and well executed. Analyses results evaluated by reviewer were ITT population. But analyses based on PP population gave consistent results. The primary objective of the efficacy was the complete resolution of heartburn in patients with s-GERD. The primary efficacy of both H40 mg and H20 mg was demonstrated to be superior to Placebo with statistically significant p-value based on valid statistical test. Although, the difference (about 20% improvement over Placebo in both H199/18 treatments) found in the data was lower than targeted value of 30%.

Results of the secondary efficacy objectives were supportive and consistent through time and variables.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events among all treatment groups.

IV.B STUDY 226

This study used a protocol identical to Study 225. Only certain items will be highlighted in this review.

The study design, schedule of evaluation, study population, primary objective, secondary objectives, sample size determination, evaluation criteria and statistical methodology were all identical to Study 225.

The study population consists of 349 patients (from a total of 913 screened) with s-GERD at 28 centers in the U.S. The inclusion/exclusion criteria were identical to Study 225.

Analysis Population: Patients participated could be removed from the trial at any time at their own request, because of lack of or insufficient therapeutic effect, an adverse event, or for other reasons unrelated to treatment. Distribution of randomization and disposition of patients entered into trial are given in the following Table IV.A.2. The ITT population included all patients randomized to treatment, with no exclusion. In the PP population, patients excluded because of study exclusion criteria, compliance violations, prohibited concomitant medications, etc. The percentage of exclusion in PP population was 9% and was evenly distributed among the three treatment groups.

Table IV.B.1 Distribution and Disposition of Patients Entered into Study 226

Screened N=913				
Not Enrolled = 564				
	H 199/18 40 mg	H199/18 20 mg	OME 20mg	Total
Randomized (ITT Population)	118	113	118	349
Completed	113	101	106	320
Not Completed	5	12	12	29
Adverse Event	1	4	3	8
Sponsor/Investigator Decision	2	3	2	7
Lost to Follow-Up	2	1	1	4
Consent Withdraw	0	3	1	4
Lack of Therapeutic Response	0	1	5	6
Safety Population (Rec'd at least 1 dose)	116	112	117	345
Per Protocol Population	106	103	109	318

Baseline measurements: The three treatment groups were well balanced with respect to all demographic, disease and other baseline characteristics collected in the study including gender, age, race, LA classification, GERD history, heartburn, acid regurgitation, dysphasia epigastric pain and *H. pylori status*.

Efficacy:

The primary objective – The proportion of patients with complete resolution reporting no heartburn by the end of trial was 36.4%, 41.6% and 11.9% for treatment with H40, H20 and Placebo respectively in ITT population. There was a statistically significant difference between H40 and Placebo ($p<0.001$), as well as between H20 and Placebo ($p<0.001$) (Table IV.B.2). The therapeutic gain about 25% -30% in each of the H199/18 treatment groups over Placebo group was near the targeted efficacy of 30%. The results of PP population were consistent with ITT population. There was no statistically significant difference between H40 group and H20 group.

Table IV. B.2[a] Complete Resolution of Heartburn As Recorded on the Diary Card, ITT Population, Study 226

	H40 mg qd	H20 mg qd	Placebo qd
Primary Objective (Reports at Final Visit)			
N	118	113	118
Complete Resolution of HB n (%)	43(36.4%)	47 (41.6%)	14 (11.9%)
Chi-Square test p-value vs. Placebo[a]	<0.001*	0.001*	
Chi-Square test p-value vs. H20 mg[b]	>0.05[b]		
Secondary Objective #1			
Week 1			
N	116	112	116
Complete Resolution of HB n (%)	22(19.0%)	17 (15.4%)	1 (0.9%)
Chi-Square test p-value vs. Placebo	<0.001*	<0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		
Week 2			
N	116	112	116
Complete Resolution of HB n (%)	41 (35.3%)	40 (35.7%)	4 (3.4%)
Chi-Square test p-value vs. Placebo	<0.001*	<0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		

Week 4			
N	115	111	116
Complete Resolution of HB n (%)	46 (40.0%)	46 (41.4%)	13 (11.2%)
Chi-Square test p-value vs. Placebo	<0.001*	<0.001*	
Chi-Square test p-value vs. H20 mg	>0.05[b]		

a: Sponsor's Table 14.2.1 and Table 14.2.3 with modification
*: Statistically significant with p-value < 0.025 of chi-square test for primary objective; and with p-value<0.05 of chi-square test with secondary objectives. It is a correction to the sponsor's legend.
b: Reviewer's Post Hoc Analysis.

The secondary objectives –

1. The proportion of patients that reported complete resolution of HB increased over time in all three treatment groups. At each time point, the resolution proportion of both H199/18 treatment groups were significantly higher than the placebo group with the largest p-value being <0.001 (Table IV.B.2). However, there was no statistically significant difference between H40 and H20 group at Week 1, Week 2 Week 4 and the final visit.
2. Proportion of relief of HB per diary card increased with time in all treatment groups. The proportions of H40 mg qd and H20 mg qd were greater than Placebo qd group at each of Weeks 1,2 and 4 and at final visit. The difference was all statistically significant using chi-square test (Table IV.B.3).

Table IV. B.3[a] Relief of Heartburn As Recorded on the Diary Card, ITT Population, Study 226

	H40 mg qd	H20 mg qd	Placebo qd
Week 1			
N	116	112	116
Relief of HB n (%) 95% CI	34 (29.3%) (21.0%, 37.6%)	31 (27.6%) (19.4%, 36.0%)	3 (2.6%) (0.1%, 5.5%)
Chi-Square test p-value vs. Placebo	<0.001*	0.001*	
Week 2			
N	116	112	116
Relief of HB n (%) 95% CI	47 (40.5%) (31.6%, 49.5%)	52 (37.2%) (37.2%, 55.7%)	10 (8.6%) (3.5%, 13.7%)
Chi-Square test p-value vs. Placebo	0.001*	0.001*	
Week 4			
N	115	111	116
Relief of HB n (%) 95% CI	55 (47.8%) (38.7%, 57.0%)	58 (52.3%) (43.0%, 61.5%)	17 (14.7%) (8.2%, 21.1%)
Chi-Square test p-value vs. Placebo	<0.001*	<0.01*	
Final Visit			
N	118	113	118
Complete Resolution of HB n (%) 95% CI	54 (45.8%) (43.0%, 54.8%)	58 (51.3%) (42.1%, 60.5%)	18 (5.3%) (8.8%, 21.7%)
Chi-Square test p-value vs. Placebo	<.001*	<.001*	

a: Sponsor's Table 14.2.4 with modification
*: Statistically significant with p-value < 0.05 of chi-square test.

3. The percentage of days without HB per diary card increased with time in all three treatment groups. The mean percentages of H40 mg qd and H20 mg qd groups were higher than the Placebo qd group at each of Weeks 1, 2 and 4. The differences were all statistically significant (Table IV.B.4).

Table IV. B.4[a] Percentage of Heartburn-Free Days As Recorded on the Diary Card, ITT Population, Study 226

	H40 mg qd	H20 mg qd	Placebo qd
Week 1			
N	116	112	116
Mean (SD)	46.2 (38.7)	49.4 (36.8)	20.7 (26.3)
p-Value vs Placebo ANOVA	<0.001*	<0.001*	
Week 2			
N	115	110	112
Mean (SD)	59.0 (39.4)	63.8 (37.2)	28.2 (32.2)
p-Value vs Placebo ANOVA	<0.001*	<0.001*	
Week 4			
N	114	102	106
Mean (SD)	66.4(36.2)	68.0 (38.2)	36.2 (35.8)
ANOVA p-Value, compared to Placebo	<0.001*	<0.001*	

a: Sponsor's Table 14.2.6 with modification
*: Statistically significant with p-value < 0.05.

4. The mean severity of HB were lower of the two H199/18 groups in comparison to the Placebo group at Week 1, 2, 4 and at the final visit. The differences were all statistically significant with p-value <0.001 using two-way ANOVA.
5. The percentage of heartburn-free nights was greater in H40 mg and H20 mg groups than the Placebo group at Week 1, 2 and 4. The differences were all statistically significant with p-value <0.001 using ANOVA.
6. The time to first resolution of HB, nocturnal HB and the time to sustained resolution of HB and nocturnal HB were shorter in H40 and H20 group than the Placebo group. All differences were statistically significant using Log-rank test. The time to first nocturnal heartburn was also shorter in H40 mg and H20 mg groups than the Placebo group. The differences were statistically significant.
7. Results of investigator-assessed resolution of heartburn and acid regurgitation at Week 2 and Week 4 were all improved for H40 and H20 over the Placebo group. All the differences were statistically significant using Cochran-Mantel-Haenszel test stratified by baseline rating of the symptoms.
8. Results of investigator-assessed resolution of dysphasia and epigastric pain at Week 2 and Week 4 were not significantly better for either H40 or H20 over Placebo.
9. Each patient's assessment of overall treatment evaluation (OTE) were combined into a 15 point scale (ranging from "A very great deal worse" to "About the same" to " A great deal better") were analyzed. The distributions of OTE based on the 15 point scale of H40 mg and H 20 mg were compared with Placebo using a Wilcoxon rank sum test. Both H40 mg and H20 groups ranked OTE showed a significantly higher preference than the Placebo group with p<0.001 at Week 2 as well as Week 4.

Primary Efficacy by Subgroup:

Relative treatment effects were similar for each gender, although male patients appeared to respond more favorably to the H40 and PL treatments. There was a lower response rate observed in patients < 65 years of age than the older age group. Given the small number of patients 65 years of age or more, the difference was not statistically meaningful. There was no noticeable difference between Caucasian and Black patients.

The presence of *H. pylori* at baseline appeared to improve the chance of complete resolution of HB in Placebo. However, the presence of *H. pylori* lowered the improvement rate in H199/18 treatment groups (Table IV.B.5).

Table IV.B.5 Proportion of Patients with Complete Resolution of Heartburn at Final Visit by *H. pylori* Status at Baseline

Resolution of HB	H40 [n=118]	H20 [n=113]	Placebo [n=118]
***H. pylori* Negative Patients**			
N	87	69	80
Resolved	34 (39.1%)	31 (44.9%)	7 (8.8%)
Not Resolved	53 (60.9%)	38 (55.1%)	73 (91.3%)
***H. pylori* Positive Patients**			
N	30	43	29
Resolved	9 (30.0%)	15 (34.9%)	7 (18.4%)
Not Resolved	21 (70.0%)	28 (65.1%)	31 (81.6%)

Safety and Tolerability:

Serious Adverse Events – There was 4 serious adverse events: 3 in H40 mg and 1 in Placebo. All cases was unlikely related to medication by investigator's assessment.

Adverse Events – There was no meaningful difference in proportion of AE between the three treatment groups (40.2% to 43.1% of patients had at least one AE in each group). Most frequent adverse events were headache, abdominal pain, diarrhea, gastrin serum increased and nausea. There was no meaningful distribution difference among the three groups.

Reviewer's Comments

Clinical trial Study 226 is the second critical multicenter studies submitted by the sponsor of this NDA in support of the approval of "treatment of symptomatic gastroesophageal reflux disease (s-GERD)". According to the sponsor, the recommended dose is 20 mg once daily for 4 weeks. Study 226 randomized 349 patients into treatment arms, H199/18 40 mg, H199/18 20 mg and Placebo. The study was well planned, well conducted and well executed. Analyses results evaluated by reviewer were ITT population. But analyses based on PP population gave consistent results. The primary objective of the efficacy was the complete resolution of heartburn in patients with s-GERD. The primary efficacy of both H40 mg and H20 mg was demonstrated to be superior to Placebo with statistically significant p-value based on valid statistical test. The difference (about 25%-30% improvement over Placebo in H199/18 treatments) found in the data was near than targeted value of 30%.

Results of the secondary efficacy objectives were supportive and consistent through time and variables.

Results of the safety analyses of this study demonstrated that there was no statistically meaningful difference in distribution of adverse events between the tywo treatment groups.

IV.C SUPPORTIVE TRIALS (STUDY SH-QBE-0009, STUDY SH-QBE-011, STUDY SH-QBE-021)

All three studies were designed will OME 20 mg as active control treatment. Study SH-QBE-0009 was a 4-week treatment trial comparing the efficacy of H40 mg, H20 mg with OME20 mg. Study SH-QBE-0011 was a 4-week treatment trial to compare the efficacy of H40 mg with OME20 mg. Study SH-QBE-021 was a 4-week treatment trial to compare the efficacy of H20 mg with OME 20 mg. All three studies failed to demonstrate superiority of H199/18 over OME20 mg.

IV.D REVIEWER'S SUMMARY OF CLINICAL TRIALS IN SUPPORT OF TREATMENT OF SYMPTOMATIC GERD

Study 225 and Study 226 had identical protocol. Both were well designed with proper randomization scheme, double blind, multicenter, placebo-controlled, parallel group 3-arm and appropriate sample sizes. In both studies, the efficacy of both H40 mg and H20 mg were demonstrated by the statistically significant superiority over Placebo in the percentage of complete resolution of heartburn. The evidence was also supported by the statistically significant improvement over placebo in all secondary s-GERD objectives. The difference was shown at Week 1, Week 2, Week 4 and at the final visit.

The reviewer agrees with the sponsor's conclusion that, in 4-week treatment, there was statistically significant evidence of the efficacy of H199/18 40 mg and H199/18 20 mg for treatment of symptomatic GERD.

In Study 225 and Study 226, there was some observed efficacy difference (due probably to small size) in the following subgroups: gender, age and race. The presence of H. pylori appeared to improve the chance of complete resolution of HB in all three treatments. However, the results were not replicated in H199/18 treatment groups in Study 226.

The reviewers also agrees with the sponsor's conclusion that, in this 4-week study, there were clear differences between H199/18 treatment groups and the Placebo group in the occurrence of adverse events.

In these two studies, for both primary and secondary objectives, the data did not demonstrate increased benefit between H20 mg and H40 mg.

V. REVIEWER'S SUMMARY OF NDA21135

V.A INTEGRATED EFFICACY FOR THREE INDICATIONS

This NDA contains eleven clinical studies in support of the treatment of H199/18 for three indications, a) healing of erosive esophagitis, b) maintenance of healing of erosive esophagitis, c) treatment of s-GERD.

a) Healing of erosive esophagitis

For this indication, the support of the sponsor's claim was in the two pivotal clinical trials, Study 172 and Study 222. The efficacy of H199/18 was demonstrated by the statistical superiority of H40 mg over OME 20 mg in both of Study 172 and Study 222. The failure of showing superiority of H20 mg over OME 20 mg in Study 172 and Study 174 did not lead to the conclusion that H20 mg is not an effective treatment. On the contrary, because of the larger percentage of healing of H20 mg over OME20 mg observed consistently in both studies, the sponsor suggested that H20 mg is an effective treatment. The evidence that the efficacy of H40 mg was not different from H20 mg significantly also supported this. Hence, the reviewer will leave the decision on dose recommendation to the medical reviewer. In general, there was no efficacy or safety difference by the subgroups including gender, race, age group. There was no effect of *H. pylori* status at Week 8. At Week 4 there appeared more improvement in patients with *H. pylori* presented at baseline.

b). Maintenance of healing of erosive esophagitis

For this indication, both studies submitted by the sponsor in support of the indication provided strong evidence that H199/18 is effective in maintaining reflux esophagitis healed up to six months. In Study 177 and Study 178, each of the three doses tested (H10, H20 and H40) was shown to be superior to Placebo.

The difference in efficacy between H10 mg and either H20 mg or H40 mg was statistically significant. On the other hand, inconsistency between two studies on the difference between H40 mg and H20 mg (H40-H20=9.2% in Study 177, = 0.4% in Study 178) made the efficacy difference between the two doses weak. Hence, the reviewer will leave the decision on dose recommendation of this indication to the medical reviewer.

There did not appear to be any relationship of GELUSIL use to H199/18 dose or duration in H199/18 treatment groups. There was no meaningful effect on maintenance due to other subgroup factors such as race, age group, LA classification, severity at baseline. Male patients appeared to have a lower rate of maintenance of healing of EE and a higher rate of recurrence than female in Study 178. But it was not replicated in Study 177.

c) Treatment of s-GERD.

For this indication, the two pivotal studies Study 225 and Study 226 submitted by the sponsor provided strong evidence that H199/18 is more effective than placebo in the treatment of s_GERD. Both H40 mg and H20 mg were shown to be superior to Placebo. The efficacious difference between H20 and H40 was not shown in any of the two studies.

V.B INTEGRATED SAFETY FOR THREE INDICATIONS

In general, for any of the three indications, H199/19 treatment was safe and tolerable at the dose level of H40 mg, H20 mg or H10mg. The most frequent adverse events were headache, abdominal pain, diarrhea, gastrin serum increased and nausea.

There was no obvious difference by subgroups such as gender, race and age group.

VI. REVIEW CONCLUSION

The data of Nda 21-153 for Nexium™ (esomeprazole magnesium, H199/18), submitted for the following three indications, provided adequate evidence in supporting of the efficacy for the three indication.

1. Healing of erosive esophagitis
2. Maintenance of healing of erosive esophagitis
3. Treatment of symptomatic gastroesophageal reflux disease.

/S/ 10/3/00
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Original : NDA
HFD-715/ENevius/Mwelch/TPermut
HFD-705/SMachado/YTsong
HFD-715/HFD-705/Chron file copy
HFD-180/LTalarico/L~~Zhou/AShaw~~/MWalsh/Division file /S/
YT/yt pp. 38, October 3. 29, 2000.

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