CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-689

STATISTICAL REVIEW(S)

06/23/04

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

SECONDARY STATISTICAL REVIEW
CLINICAL STUDIES

NDA/Serial Number:	21689
Drug Name:	Nexium® I.V. (esomeprazole sodium) for Injection
Indication(s):	Short term (up to 10 days) [redacted] of [redacted] (GERD) [redacted] patients [redacted] not possible.
Applicant:	AstraZeneca LP
Date(s):	Electronic submission received 9/10/2003.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Stella Grosser, Ph.D.
Medical Division:	Gastrointestinal and Coagulation Drug Products
Medical Reviewer:	Gail Moreschi, MD.
Project Manager:	Melissa Furness

Statistical keywords: Clinical studies; NDA review; non-inferiority

In this review I comment on the analysis of certain pharmacodynamic data presented in four acid output studies (SH-NEP-0011, SH-NEP-0012, D9615C00013, and D9615C00014) submitted in support of the intravenous formulation of esomeprazole, specifically the maximal acid output (MAO) measured 23-24 hours post-dose. The applicant presents some of this data in the proposed label (essentially, Table [1] below); the study report, however, contains a more in-depth analysis and discussion that may be relevant to a regulatory decision. Note that no independent statistical analysis of these data was performed by any statistical reviewer at the FDA.

For each of the four cross-over studies of acid output, the applicant calculates the mean MAO values for patients receiving iv or oral esomeprazole, and compares them. The label claims that mean values for the iv formulation were " [redacted] than those for the oral formulation but both showed [redacted] from published mean values for untreated GERD patients.

The applicant also provides a more formal statistical comparison of MAO across the two formulations. A non-inferiority hypothesis testing approach is used, with a margin based on the results of a published study intended to establish pharmacodynamic bio-equivalence of the iv and oral formulations of pantoprazole. To satisfy the statistical assumptions of this approach, confidence limits are calculated around regression-adjusted geometric means of MAO values. The ratio between these iv and oral geometric mean values is presented and the 95% upper confidence limit around this ratio is compared to the pre-specified limit of 1.25.

As indicated in the applicant's Table [2], the inferiority analysis results fail to reject the null hypothesis of inferiority of iv to oral esomeprazole, in the sense that the upper confidence bound for iv esomeprazole is larger than 1.25 times that of oral.

However, the clinical relevance of the proposed limits, observed differences and observed confidence bounds leading to the inferiority results is not known.

Details are given below, from the applicant's study report.

Applicant's analysis

The applicant writes, in the study report (Astra-Zeneca Document GI.000-010-796, 2.7 Clinical Summary, pp. 21-22):

> The purpose of the acid output studies in sGERD patients (SH-NEP-0011, SH-NEP-0012, D9615C00013 and D9615C00014) was to show that the effect on MAO of esomeprazole administered iv as a 3-minute injection or a 15-minute infusion is not inferior to the effect on MAO of esomeprazole administered orally.
>
> Previous data suggest that the distribution of MAO is log-normal (Metz et al 2000); hence, the analysis of MAO was based on log-transformed data. The null hypothesis was that the least squares (LS) geometric mean ratio of MAO values (iv versus oral) is ≥ 1.25 (iv inferior to oral), while the alternative hypothesis was that the LS geometric mean ratio is < 1.25 (iv not inferior to oral). The value 1.25 was based on the results of a published

study designed to establish the pharmacodynamic bio-equivalence of the iv and oral formulations of pantoprazole (Metz et al 2000). Rejecting the null hypothesis, with a significance level of 0.05, was equivalent to the 1-sided upper limit of 95% confidence of the LS geometric mean ratio of MAO values (iv versus oral) being < 1.25. Therefore, if the 1-sided 95% upper confidence limit of the LS geometric mean ratio of MAO values (iv versus oral) was < 1.25, the pharmacodynamic non-inferiority of the iv formulation to the oral formulation would be statistically confirmed. The primary efficacy variables for evaluation were MAO measured 23-24 hours after the last dose of 10days of oral and iv dosing, respectively.

... [L]og-transformed MAO was analyzed using a mixed model analysis of variance (ANOVA) with effects for sequence, patient (sequence), period, and formulation. First, the means and the 95% confidence intervals (CIs) for each formulation and the mean differences between formulations and their 1-sided upper limit of 95% confidence were estimated. These estimates were then anti– logarithmized to obtain the LS geometric means of MAO for each formulation and their 95% CIs, as well as the LS geometric mean ratios of MAO (iv versus oral) and their 1-sided upper limit of 95% confidence.
...

and discusses the results (*Ibid*, pp 57 – 59):

The effect of once daily iv and oral administration of esomeprazole for 10 days was investigated in 4 studies in sGERD patients, with or without EE. Two of the studies used the 20 mg dose of both formulations, while the other 2 studies used the 40 mg dose. The iv formulation was administered as a 3-minute injection in 2 of the studies, and as a 15-minute infusion in the other 2 studies.

Across all 4 acid output studies, repeated iv and oral administration of esomeprazole in sGERD patients, with or without EE, resulted in mean MAO values ranging from 3.52 mmol/h to 5.06 mmol/h for the 40 mg dose and from 5.26 mmol/h to 5.96 mmol/h for the 20 mg dose (Table [1]). The corresponding LS geometric mean values were somewhat lower (Table [2]).

Table [1] Mean (SD) MAO measured 23-24 hours post-dose following once daily iv and oral administration of esomeprazole for 10 days in sGERD patients with or without EE (PP population)

Study	Dose	IV administration method	MAO (mmol/h)	
			IV	Oral
SH-NEP-0011 (n=47)	40 mg	15-minute infusion	4.74 (3.65)	3.52 (2.86)
SH-NEP-0012 (n=44)	20 mg	15-minute infusion	5.95 (4.00)	5.26 (4.12)
D9615C00013 (n=50)	40 mg	3-minute injection	5.06 (3.90)	4.41 (3.11)
D9615C00014 (n=42)	20 mg	3-minute injection	5.96 (5.41)	5.27 (5.39)

It has previously been reported that in a similar population of untreated GERD patients with or without EE, mean MAO was 34.9 mmol/h and 30.7 mmol/h, respectively, for males and 19.2 mmol/h and 18.7 mmol/h, respectively, for females (Hirschowitz 1991). Similar mean MAO values for untreated GERD patients have been reported elsewhere (Cadiot et al 1994). The markedly lower mean MAO values observed in the present studies indicate that both iv and oral administration of esomeprazole result in a pronounced reduction (approximately 70%-90%) in pentagastrin-stimulated MAO.

Table [2] LS geometric mean (95% CI) and LS geometric mean ratio (1-sided upper 95% CI) for MAO measured 23-24 hours post-dose following once daily iv and oral administration of esomeprazole for 10 days in sGERD patients with or without EE (PP population)

Study	Dose	IV administration method	MAO (mmol/h)		
			IV	Oral	Ratio IV/Oral
SH-NEP-0011 (n=47)	40 mg	15-minute infusion	3.02 (2.08:4.36)	2.24 (1.55:3.25)	1.35 (1.71)
SH-NEP-0012 (n=44)	20 mg	15-minute infusion	4.11 (2.77:6.12)	3.29 (2.21:4.90)	1.25 (1.58)
D9615C00013 (n=50) [a]	40 mg	3-minute injection	3.88 (2.76:5.47)	2.75 (1.97:3.85)	1.41 (1.82)
D9615C00014 (n=42)	20 mg	3-minute injection	3.44 (2.36:5.00)	3.18 (2.18:4.65)	1.08 (1.44)

[a] 3 patients (1018, 1045 & 3005) had zero MAO (pH>7 in all gastric samples) after iv administration and were excluded in the statistical analysis for iv (n=47).

The observed mean MAO values were higher after iv administration compared to oral administration in all studies, with no evident differences between 3-minute injection and 15-minute infusion (Table [1]). Furthermore, the statistical criterion for pharmacodynamic non-inferiority (ie, 1-sided upper 95% confidence limit of the LS geometric mean ratio, iv/oral, < 1.25) was not met in any of the studies (Table [2]). However, the differences between the observed mean MAO values for iv and those for oral administration were small, relative to the mean MAO values reported for untreated EE and non-EE patients presented above (19.2-34.9 mmol/h and 18.7-30.7 mmol/h, respectively, with a difference between female and male patients of more than 10 mmol/h; Hirschowitz 1991).

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Stella Grosser
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BIOMETRICS
secondary statistical review of MAO data

06/18/04

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 21689

Drug Name: Nexium® I.V. (esomeprazole sodium) for Injection
Indication(s): Short term (up to 10 days) [redacted] of [redacted] [redacted] (GERD) [redacted] patients [redacted] is not possible.
Applicant: AstraZeneca LP
Date(s): Electronic submission received 9/10/2003.
Review Priority: Standard

Biometrics Division: Division of Biometrics II
Statistical Reviewer: Wen-Jen Chen, Ph.D. (HFD-715)
Concurring Reviewers: Stella Grosser, Ph.D. (HFD-715)

Medical Division: Gastrointestinal and Coagulation Drug Products
Medical Reviewer: Gail Moreschi, MD.
Project Manager: Ms. Melissa Furness

Statistical Keywords: Clinical studies; NDA review.

TABLE OF CONTENTS

1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

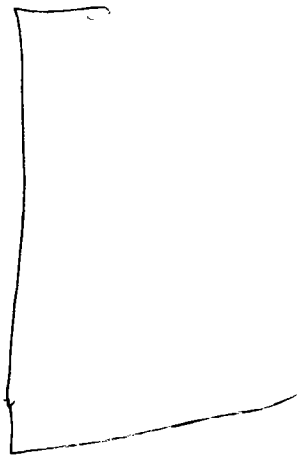
1.2 Brief Overview of Clinical Studies

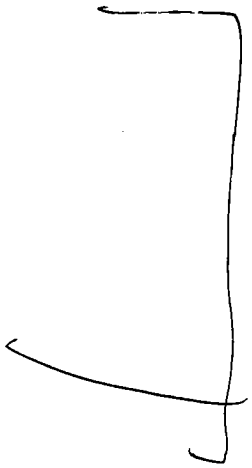
In this NDA submission, the sponsor has submitted five Phase III studies to support the use of intravenous (iv) esomeprazole for short term (up to 10 days) treatment of gastroesophageal reflux disease (GERD) in patients for whom oral administration is not possible. However, noted by this reviewer, of the five Phase III studies, the four studies SH-NEP-0011, SH-NEP-0012, D9615C00013, and D9615C00014 are the pharmacology (pharmacodynamic) studies in GERD patients with or without erosive esophagitis and one study SH-NEP-0006 is the clinical safety study. As a result, in this review, the clinical safety study SH-NEP-0006 is the focus.

1.3 Statistical Issues and Findings

For Study SH-NEP-0006, the following four issues are identified and commented upon:

1)





2) Quality of the erosive esophagitis assessments

It is noted that after the first week of randomized treatment period, an open label treatment period of three weeks was followed. In the open label period with three treated arms (esomeprazole 40 mg iv 3 min, esomeprazole 40 mg iv 30 min., and esomeprazole 40 mg orally), it was very possible for the investigator to assign similar scores (LA Classification system: graded A-D) to the patients in the three treatment groups as healing assessments for erosive esophagitis. Since the assessments may be subjective, if investigators assessed the healing outcomes of the erosive esophagitis for the three treatment groups as close as possible, then, the chances of equivalence/comparability on the healing rates of erosive esophagitis for all three treatment groups (esomerprazole 40 mg iv 3 min, esomerprazole 40 mg iv 30 min, and esomerprazole 40 mg orall) would be greatly increased. Thus, the comparability of the healing rates for the three treatment groups established by the above assessments is possibly biased.

3) Severity of erosive esophagitis for the enrolled patients

Note that less than a quarter (23%; 25/246) of enrolled subjects had erosive esophagitis with more severe LA grades C and D at baseline and the largest minority of patients (greater than 40%) had mild erosive esophagitis with LA grade B (Table 16 on page 54 of Clinical Study Report submitted through the electronic system). Therefore, due to lack of sufficient enrollment of more severe esophagitis subjects, the comparison of the healing rates for esomerprazole 40 mg iv 3 min and esomerprazole 40 mg iv 30 min to that of esomerprazole 40 mg orally performed by the sponsor may not reflect the comparability of the three treatments for the patients with more severe erosive esophagitis at baseline.

4) Criteria used for the clinical equivalence analysis

It is noted that instead of using a pre-specified delta margin as stated by E10, "Guidance for Industry, E10 choice of Control Group and Related Issues in Clinical Trials", the conclusion of the clinical equivalence between esomeprazole

oral and esomeprazole iv made by the sponsor was based upon the intuitive judgment on the closeness of healing rates presented in sponsor's Table 14 and the 95% confidence intervals for the differences of healing rates on erosive esophagitis between esomeprazole iv and oral administrations presented in sponsor's Table 15. Accordingly, the comparable analysis on the healing rates of the erosive esophagitis for the three treatment groups (esomeprazole 40 mg iv 3 min., esomerprazole 40 mg iv 30 min., and esomeprazole 40 mg orally) performed by the sponsor is not statistically adequate.

2.0 INTRODUCTION

2.1 Overview

With regard to Nexium (esomeprazole sodium), the sponsor made the following observations:

> GERD, generally a chronic disease, is defined by reflux of gastric content into the esophagus, leading to mucosal breaks and/or symptoms such as heartburn, upper abdominal pain, regurgitation, and dysphagia. GERD has a prevalence in western countries of about 6% to 7% (Wienbeck and Barnert 1989); and approximately 50% of these patients have esophageal mucosal breaks.
>
> Esomeprazole is the single (*S*)-enantiomer of the proton pump inhibitor (PPI) omeprazole, and acts through inhibition of the proton pumping enzyme H+/K+-ATPase located in the parietal cells of the gastric oxyntic mucosa, thus preventing hydrochloric acid secretion to the gastric lumen. The oral formulation of esomeprazole (20 mg and 40 mg) was approved in the US in February 2001. The approved indications are GERD and eradication of *Helicobacter pylori* in combination with an appropriate antibacterial therapeutic regimen. AstraZeneca has developed an intravenous (iv) formulation of [redacted] (esomeprazole, NEXIUM®) [redacted]

In this NDA submission, the sponsor has submitted five Phase III studies to support the use of intravenous (iv) esomeprazole for short term (up to 10 days) [redacted] of [redacted] (GERD) [redacted] patients [redacted] is not possible. However, noted by this reviewer, of the five Phase III studies, the four studies SH-NEP-0011, SH-NEP-0012, D9615C00013, and D9615C00014 are the pharmacology (pharmacodynamic) studies in GERD patients with or without erosive esophagitis and one study SH-NEP-0006 is the clinical safety [redacted] study. As a result, in this review, the clinical safety [redacted] study SH-NEP-0006 is the focus.

2.2 Data Sources

This reviewer reviewed "MODULE 5 Clinical Study Reports" submitted by the sponsor through electronic system dated Sep 10, 2003 and located at "\\Cdsesub1\n21689\N_006\2003-90-10\Clinstat".

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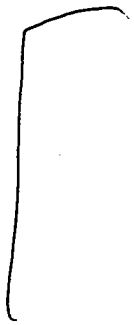

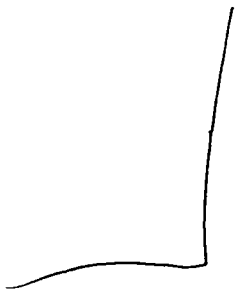

3.2 Evaluation of Safety for Study SH-NEP-0006

Among the 246 subjects, no deaths were reported, 4 subjects were reported as serious adverse events (all were unrelated to study treatment), and 3 subjects discontinued study treatment due to adverse events (AEs). All 7 subjects were randomized to the oral treatment group.

During week 1, the number of subjects who reported AEs and the number of AEs reported were similar in all treatment groups. The most common AEs during week 1 were: headache, flatulence, nausea, diarrhoea, abdominal pain, constipation, dizziness/vertigo and dry mouth. No clinically relevant difference was observed among the treatment groups in the most commonly reported AEs. A large proportion of the AEs were reported during the first week. This is most likely a result of the more frequent assessments of AEs during the first 7 days in the study, when the subjects visited the study site once daily.

When comparing the treatment groups during four-week treatment, relatively fewer AEs were reported in the groups treated with injection or infusion during week 1 compared to the oral treatment group. All SAEs reported emanated from the group treated with oral esomeprazole the first week. Both observations are probably a chance finding.

There were no indications of that the higher peak plasma concentration following intravenous administration compared to oral administration changed the pattern of AEs. No safety concerns

were raised concerning the AEs reported during this study. Esomeprazole 40 mg od iv for 7 days, as an injection or as an infusion, showed a similar AE-pattern as oral treatment with esomeprazole 40 mg od for 7 days.

4.0 SUBGROUP ANALYSIS

No subgroup analyses on gender, race, and age were performed by the sponsor or this reviewer.

5.0 SUMMARY AND CONCLUSIONS

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