CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-957

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Esomeprazole Magnesium
PRODUCT (Proposed Brand Name):	**NEXIUM®**
DOSAGE FORM:	For Delayed-Release Oral Suspension
DOSAGE STRENGTH:	20/40 mg packets
NDA:	21- 957
PROPOSED INDICATIONS:	Gastroesophageal Reflux Disease (GERD)
NDA TYPE:	505(b) (2)
SUBMISSION DATE:	December 22, 2005
SPONSOR:	AstraZeneca LP
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Suliman I. Al-Fayoumi, Ph.D.
OCPB DIVISION:	DCP III, HFD 880
OND DIVISION:	HFD180

1. Executive Summary

Esomeprazole magnesium (hereafter referred to as esomeprazole) is a proton-pump inhibitor (PPI), which works through an inhibition of the final step in the production of gastric acid by selective inhibition of the H+/K+ ATPase located in the secretory membranes of the parietal cells in the gastric oxyntic mucosa. Esomeprazole is the pure S-enantiomer of the racemic omeprazole. Esomeprazole has been on the market as NEXIUM® since March 2000 (Sweden) and is, as of 30 September 2005, approved in 105 countries world-wide. NEXIUM is approved for the treatment of various acid-related disorders, such as symptomatic treatment of gastroesophageal reflux disease (GERD) and healing of erosive reflux esophagitis, including prevention of esophagitis relapse. In addition, NEXIUM is indicated in combination with an appropriate antibacterial therapeutic regimen for the eradication of *Helicobacter pylori* infection in patients with duodenal ulcer disease and for the risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer. NEXIUM is developed for both oral and intravenous administration, where oral administration presently includes delayed release capsules (US) and delayed-release tablets (all countries other than US).

The current application provides documentation supporting the use of a pellet-based sachet formulation of esomeprazole as a new oral dosage form of NEXIUM. The sachet formulation is aimed as an alternative to the capsule formulation for all currently approved indications of NEXIUM.

The pellet-based sachet formulation is a new formulation of esomeprazole that can be administered orally (for example by drinking and syringe) or by administration via nasogastric and gastric tubes. It consists of 2 drug product intermediates, esomeprazole delayed release granules (hereafter denoted as esomeprazole pellets) and excipient granules for oral suspension (hereafter denoted as excipient granules), which are filled in a single-use child resistant aluminium packet (hereafter denoted as a sachet). Prior to administration the full contents of 1 sachet are added to water to form a viscous suspension. The suspension is suitable for administration by spoon, drinking or through enteric tubes.

The primary package is a sachet made from an aluminium laminate, where the aluminium layer provides a moisture barrier. The composition of the laminate from the outside to the inside is the following: [redacted]. The size of the sachet is identical for all strengths. The filled sachets are packed in a carton.

According to the sponsor, the sachet formulation is intended as an appropriate formulation for all patients who have difficulty swallowing a capsule. The large drug administration flexibility allowed with the sachet formulation will facilitate treatment of some patients who currently are referred to treatment with NEXIUM as a capsule. The sachet formulation will meet the medical need of an oral esomeprazole formulation for the diverse group of patients including patients who have esophageal structural anomalies (esophageal strictures, diverticuli, etc.), suffer from esophageal dysmotility characterized

by dysphagia, or have functional swallowing disorders. Other potential users of the sachet formulation include geriatric and pediatric patients, and those patients who receive nutrition and medication through feeding tubes. Lastly, there are patients who simply prefer or require an alternative to a solid drug formulation.

The sachet formulation consists of the same enteric-coated pellets of esomeprazole as the capsule formulation. Besides these acid-stabile pellets, the sachet formulation contains inactive excipient granules. The contents of the sachet are to be mixed with water and the suspension can be left for up to 30 minutes before administration.

The sachet formulation of esomeprazole has been developed as [redacted] strengths: [redacted] 20, and 40 mg; however only 20 mg and 40 mg strengths are subject to approval in this application. The proposed changes to the Package Insert (PI) for NEXIUM will provide information on the sachet as an alternative administration option for the currently approved capsule indications (the 20 and 40 mg strengths only). [redacted]

The NEXIUM sachet clinical development program is limited to one study (D9612C00032) with the primary objective of showing bioequivalence between the approved and commercially available oral formulations (the capsule and tablet) and the new pellet-based sachet formulation. The bioequivalence study is of an open-label, randomized, 3-way crossover design comparing single doses of esomeprazole 40 mg under fasting conditions. The clinical documentation for the sachet application includes data from 96 healthy subjects, 20 to 50 years of age. Since only the comparison with the capsule formulation is relevant in this application, the following discussion does not include the tablet formulation.

The single esomeprazole 40 mg dose, which is the highest approved dose of NEXIUM, was chosen for the bioavailability and bioequivalence study. In addition, for all the lower strengths of the sachet formulation, the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidance, up to and including Level II, which provide further justification for the choice of the esomeprazole 40 mg dose in the conducted *in vivo* bioequivalence study. The new sachet formulation was shown to be bioequivalent to approved oral capsule formulation of NEXIUM.

As mentioned earlier, this application includes no clinical trials. The firm proposed a dissolution procedure which subsequently was modified later by the sponsor and acceptable by the CMC and CP offices. Dissolution profiles using the sponsor's proposed method were evaluated for the [redacted] 20 mg delayed-release sachets compared to the 40 mg delayed-release sachets used in the bioavailability studies (biolot). This data was used to support a biowaiver for the 20-mg sachets.

The clinical efficacy of esomeprazole administered as capsule was presented in the original application for NEXIUM (NDA 21-153). Efficacy data on the new sachet

formulation are not considered necessary due to the established bioequivalence between the capsule and sachet formulations. The previously submitted efficacy data for esomeprazole are considered to be applicable to the current application as well.

The following clinical pharmacology and biopharmaceutics information was submitted in this application:

1. The firm conducted a bioequivalence study under fasting conditions comparing the highest proposed strength (40 mg) of NEXIUM® for Delayed-Release Granules for Oral Suspension to the approved 40-mg NEXIUM® for Delayed-Release Capsules reference product .
2. A waiver for the lower strength 20-mg strength NEXIUM® for Delayed-Release Granules for Oral Suspension was requested based on formulation proportionality, linear pharmacokinetics and similarity of the dissolution profiles compared to the 40-mg NEXIUM® Delayed-Release Granules for Oral Suspension (biolot) using a single dissolution procedure.
3. The sponsor used the same validated analytical method to determine the level of esomprazole in human plasma for both sachet and capsule formulations.
4. The sponsor's labeling reflects incorporation of the new information about sachet formulation into the original label for Nexium Capsule.

Comments

1. BIOEQUIVALENCE STUDY: The 90% CIs for the ratios (sachet/capsule) of the geometric means for AUC, AUCt and Cmax were contained in the interval 0.80 to 1.25, and thus the new pellets based sachet formulation of esomeprazole is considered to be bioequivalent to the commercial capsule of esomeprazole 40 mg.

2. WAIVER FOR LOWER STRENGTHS: A waiver for the lower strength 20-mg strength sachet was requested based on formulation proportionality and similarity of the dissolution profiles compared to the 40-mg esomeprazole capsules (biolot) and it is acceptable.

3. DISSOLUTION SPECIFICATION: The sponsor's dissolution method and revised specification (Not less than [redacted] (Q) of label claim of Esomeprazole released at pH 6.8 buffer preceded by exposure of the drug product to 0.1 M hydrochloric acid for 2 hours using a USP apparatus 2 (paddle at 100 rpm, 37°C) is acceptable.

1.1 RECOMMENDATIONS

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-957 is acceptable with the suggested labeling changes described in Section 3.

1.2 Phase IV commitments: None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Esomeprazole magnesium (hereafter referred to as esomeprazole) is a proton-pump inhibitor (PPI), which works through an inhibition of the final step in the production of gastric acid by selective inhibition of the H+/K+ ATPase located in the secretory membranes of the parietal cells in the gastric oxyntic mucosa. NEXIUM Delayed-Release Capsules was approved by the FDA in 2001 under NDA 21-153/21-154. The same sponsor (Astra-Zeneca) now proposes to market NEXIUM Delayed-Release Granules for Oral Suspension in 20-mg, and 40 mg strengths, which are formulated to be bioequivalent to NEXIUM Delayed-Release Capsules of same strengths.

The current application includes no clinical trials. The clinical efficacy and safety of the drug are based on the clinical information from the original NDA for NEXIUM Delayed-Release Capsules (NDA 21153/**21154**). The submission contains the following information:

1. **Bioequivalence studies (Study 032)** - A Single-Centre, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of Esomeprazole 40 mg following a Single Oral Dose under Fasting Conditions in Healthy Male and Female Subjects.

- ***Pharmacokinetics:***

1. Based on the statistical results for Nexium Sachets, the 90% confidence intervals for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation (Nexium delayed-release capsules) were found to be within the range of 0.80 – 1.25 The confidence intervals for AUC0-t, AUC0-inf, and Cmax were [0.93- 1.03], [0.93 – 1.03], and [0.84 – 0.96], respectively.

2. The ratio of the geometric least square means for AUC0-t, AUC0-inf, and Cmax are 0.98, 0.98 and 0.90, respectively.

3. No significant difference was observed for Tmax between the two treatments. The mean Tmax was 2.32 hours for the Test formulation and 2.18 hours for the Reference formulation.

4. The $t_{½}$ of two treatments were very similar. The mean $t_{½}$ was 1.09 hours for the Test formulation and 1.07 hours for the Reference formulation.

- ***Safety:*** There were no serious adverse events reported. No significant safety concerns were raised.

2. Waiver Requests

Waiver for a biostudy of the 20-mg sachets: A biowaiver was requested for the lower strengths of sachets. However, biowaiver of only 20-mg strength is under consideration in this submission. The FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" states that "Waiver of in vivo BE studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate in vivo study; and (3) the new strength meets an appropriate in vitro dissolution test. Biowaiver of the lower strengths and especially the 20-mg sachets is justified by linear kinetics, the strength proportionality and demonstrated similarity of in vitro dissolution time profiles for the [redacted] strengths. Strength proportionality, according to SUPAC MR level II, can be justified since the difference in ratios of inactive to total weight of the dosage form are within ±5% for all strengths. The similarity of the in vitro dissolution time profiles of the [redacted] strengths, [redacted] 20 mg and the 40 mg strength, see Figure 1, was determined by calculation of the similarity factor f2. The calculated similarity factors (f2) are all between 50 and 100, which suggest that the dissolution profiles of the lower strengths are similar to that of the 40 mg strength. Therefore, biowaiver for 20-mg sachets can be granted.

3. Dissolution

The *in vitro* dissolution test for Esomeprazole Sachets is identical to the methods used for the intermediate esomeprazole pellets and the approved. The method is based on the procedure described in the USP for Delayed-Release Dosage Forms, ie, first exposing the drug product to 0.1 M hydrochloric acid for 2 hours using a USP apparatus 2 (paddle at 100 rpm, 37°C) followed by determination of the *in vitro* release at pH 6.8. The amount of esomeprazole released after 30 minutes is determined by [redacted] phase liquid chromatography with UV detection at

4. Labeling

The labeling is comparable to the labeling for the approved Nexium delayed-release Capsules, with proposed revisions the Description, Clinical Pharmacology, Precautions, Dosage and Administration, and How Supplied to reflect the differences in the dosage forms.

Conclusion:

1. The sponsor has demonstrated the bioequivalence of a new 40-mg Nexium delayed-release Sachets dosage form of esomeprazole to the approved 40-mg Nexium delayed-release Capsules under fasting conditions.

2. The waiver for in vivo studies for the 20-mg sachets based on dose proportionality and similarity of the dissolution profiles compared to the 40-mg esomeprazole capsules (biolot) is acceptable.

3. The sponsor's dissolution method and revised specification (Not less than [redacted] (Q) of label claim of Esomeprazole released at pH 6.8 buffer preceded by exposure of the drug product to 0.1 M hydrochloric acid for 2 hours using a USP apparatus 2 (paddle at 100 rpm, 37°C) is acceptable.

Signatures

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

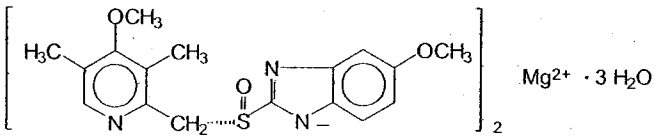
Team Leader: Al-Fayoumi, Suliman I, Ph. D._____

2. QBR

2.1. General Attributes

2.1.1. *What are the chemical and physical-chemical properties of the drug substance?*

Trade name: NEXIUM® Delayed-Release Granules for Oral Suspension (20/40 mg)
Generic name: Esomeprazole Magnesium
Chemical name: bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate
Chemical Structure:



Dosage Form Description

Each packet of NEXIUM for Delayed-Release Oral Suspension contains 20 mg or 40 mg of esomeprazole, in the form of the same enteric-coated pellets used in NEXIUM Delayed-Release Capsules, and also inactive granules. The inactive granules are composed of the following ingredients: dextrose, xanthan gum, crospovidone, citric acid, iron oxide, and hydroxypropyl cellulose. The esomeprazole granules and inactive granules are constituted with water to form a suspension and are given by oral, nasogastric or gastric administration.

The composition of the different strengths of Esomeprazole Sachets is presented in the following Table 1.

Table 1: Composition of Esomeprazole Sachets

Components	Quantity (mg/sachet)	
	20 mg	40 mg
Esomeprazole pellets		
Esomeprazole	20	40
Glycerol monostearate 40-55	[redacted]	[redacted]
Hydroxypropyl cellulose	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]
Methacrylic copolymer type C	[redacted]	[redacted]
Polysorbate 80	[redacted]	[redacted]

Sugar spheres, [redacted]			
Talc			
Triethyl citrate			
[redacted]			
Weight of Esomeprazole pellets			
Excipient granules			
[redacted]			
Xanthan gum			
[redacted]			
Citric acid [redacted]			
Iron oxide, [redacted]			
Hydroxypropyl cellulose			
[redacted]			
Weight of Excipient granules			
Total weight in sachet			

2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

2.1.3. *What is the proposed route of administration?*

NEXIUM Delayed-Release Granules for Oral Suspension should be administered as follows:

- Empty the contents of a 20 mg or 40 mg packet into a container containing 1 tablespoon (15 mL) of water.
- Stir.
- Leave a few minutes to thicken.
- Stir and drink within 30 minutes.
- If any material remains after drinking, add more water, stir, and drink immediately.

2.2. Clinical Pharmacology

2.2.1. *What are the pharmacokinetics of esomeprazole?*

The sponsor added on the clinical pharmacology of Nexium Delayed-Release Capsules for this section.

Pharmacokinetics
Absorption

NEXIUM Delayed-Release Capsules and NEXIUM Delayed-Release Granules for Oral Suspension contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on day 1 to 11.2 μmol*hr/L on day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of NEXIUM over a period of five days. The results are shown in the following table:

Pharmacokinetic Parameters of NEXIUM Following Oral Dosing for 5 days

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
AUC (μmol*h/L)	12.6	4.2
Coefficient of variation	42%	59%
C_{max} (μmol/L)	4.7	2.1
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2

Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor metabolizers. At steady state, the ratio of AUC in Poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

2.2.2. *What are the dose and dosing regimen?*

The recommended adult dosages are outlined in the table below. NEXIUM should be taken at least one hour before meals.

Recommended Adult Dosage Schedule of NEXIUM

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20 mg	Once Daily**
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
Risk Reduction of NSAID-Associated Gastric Ulcer	20 mg or 40 mg	Once Daily for up to 6 months**

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
NEXIUM	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

2.2.3. *Are the pharmacokinetic parameters linear at steady-state?*

The Cmax increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg at steady state.

2.3. Intrinsic Factors

NEXIUM for Delayed-Release Oral Suspension are designed to be bioequivalent to NEXIUM Delayed-Release Capsules and the influence of any intrinsic factors would be expected to be the same as indicated for NEXIUM Delayed-Release Capsules and are reflected in the label.

2.4. Extrinsic factors

The influence of extrinsic factors and/or impact of any difference in exposure would be expected to be the same as for NEXIUM Delayed-Release Capsules. These issues are covered in the labeling in the same way as for NEXIUM Delayed-Release Capsules.

2.5. General Biopharmaceutics

2.5.1. *Was bioequivalence demonstrated for the new NEXIUM for Delayed-Release Oral Suspension when compared to the NEXIUM Delayed-Release Capsule dosage form?*

Yes, the sponsor conducted a A Single-Centre, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of Esomeprazole 40 mg following a Single Oral Dose under Fasting Conditions in Healthy Male and Female Subjects. The 40 mg esomeprazole sachet met the bioequivalence criteria when compared to 40 mg capsules. The Results are summarized below:

Variable	Treatment	N	GMR	90% CI	
				Lower	Upper
AUC(µmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03

C_{max}(µmol/L)	Sachet/Capsule	94	0.90	0.84	0.96
AUC_t(µmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03

2.5.2. ***What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type?***

The labeling for NEXIUM Delayed-Release Capsules states that "The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals." The sachet formulation consists of the same enteric-coated pellets of esomeprazole as the capsule formulation. Besides these acid-stabile pellets, the sachet formulation contains inactive excipient granules. Since NEXIUM for Delayed-Release Oral Suspension 40-mg are bioequivalent to NEXIUM Delayed-Release 40-mg Capsules under fasting conditions and in-vitro dissolution profiles of the capsules and sachet formulations are similar, no additional food effect study was necessary.

2.5.3. ***What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?***

The to-be-marketed formulation is identical to the formulation used in the pivotal clinical study.

2.5.4. ***Are the Sponsor's proposed dissolution medium and specifications acceptable?***

Yes. The *in vitro* dissolution test for Esomeprazole Sachets is identical to the methods used for the intermediate esomeprazole pellets and the Nexium Capsules. The method is based on the procedure described in the USP for Delayed-Release Dosage Forms, ie, first exposing the drug product to 0.1 M hydrochloric acid for 2 hours using a USP apparatus 2 (paddle at 100 rpm, 37°C) followed by determination of the *in vitro* release at pH 6.8. The amount of esomeprazole released after 30 minutes is determined by [redacted] phase liquid chromatography with UV detection at 302 nm.

The dissolution characteristics are related to the esomeprazole pellets. The presence of excipient granules in the drug product did not affect the dissolution profile. Dissolution profiles were analyzed for a number of combinations of esomeprazole pellets and excipient granules batches, representing the strengths [redacted] \40 mg, and the results were compared to results obtained for the esomeprazole pellets alone, see Table 1. The results with and without the presence of excipient granules for all drug product strengths are in agreement (overall result [redacted] of added amount both with and without the presence of excipient granules). [redacted]

Table 1: Dissolution (n=6) analyzed with and without the presence of excipient granules at 60 minutes

Esomeprazole pellets batch number	Excipient granules batch number	Dissolution (mean (range), % of added amount)		Mean (% of added amount)
			Strength 40 mg	
5664	Not included			
	101			
	103			
	104			
5671	Not included			
	101			
	103			
	104			
5677	Not included			
	101			
	103			
	104			
Overall mean per strength (n=12)				
Overall mean, excipient granules included (n=27)				
Overall mean, no excipients granules included (n=9)				

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

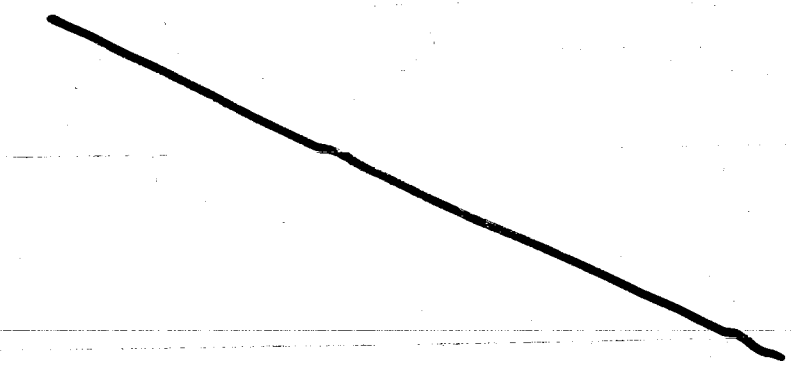
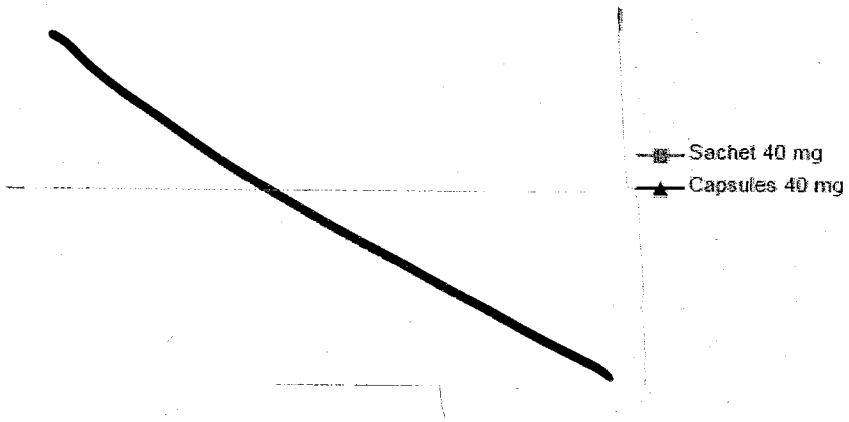


Figure 5: Mean (n=12) *in vitro* dissolution time profiles of Esomeprazole Sachets 40 mg and Nexium Capsules 40 mg at pH 6.8 after 2 h pre-exposure to 0.1 M hydrochloric acid



Based on the results, the sponsor proposed that the Q-value [redacted] be the same for Esomeprazole Sachets as used for the Nexium Capsules, since the esomeprazole pellets are the same as those used in the capsules and the dissolution profile is not affected by the presence of the excipient granules. However, based on the dissolution profiles, and the comments made by CMC and Clinical Pharmacology reviewers, the sponsor revised the *in-vitro* dissolution specification the following:

Not less than [redacted] (Q) of label claim of Esomeprazole released at pH 6.8 buffer preceded by exposure of the drug product to 0.1 M hydrochloric acid for 2 hours using a USP apparatus 2 (paddle at 100 rpm, 37°C

The above specification is acceptable.

2.6. Analytical

2.6.1. *Were the correct moieties identified and properly measured?*

Yes, samples for determination of esomeprazole in plasma were analyzed at [redacted], AstraZeneca R&D Mölndal, Sweden using validated normal-phase liquid chromatography and UV-detection according to method no. AS M-002 version 3 [redacted] implementation of AstraZeneca method no. BA-222). It was the same method used for quantitation of esomeprazole during approval of Nexium Delayed rlease capsules. The limit of quantification (LOQ) of esomeprazole was 25 nmol/L.

27 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

4.2 Individual Study

NDA: 21-957/Study 032 **Study Dates: Jan '05 – Apr '05**

A Single-Centre, Open, Randomized, Three-way Crossover Bioequivalence Study Comparing a Pellets Based Sachet Formulation of Esomeprazole with a Commercial Tablet and a Commercial Capsule of Esomeprazole 40 mg following a Single Oral Dose under Fasting Conditions in Healthy Male and Female Subjects

Objectives

The primary objective of this study was to investigate whether a new pellets based sachet formulation of esomeprazole is bioequivalent to a commercial tablet and a commercial capsule of esomeprazole following single oral doses of 40 mg, respectively, by assessment of the total area under the plasma concentration versus time curve (AUC) and the observed maximum plasma concentration (Cmax).

The secondary objectives were:

To evaluate the pharmacokinetic properties of a new pellets based sachet formulation of esomeprazole, a commercial tablet, and a commercial capsule of esomeprazole following single oral doses of 40 mg, respectively, by assessment of the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUCt), the time of observed maximum plasma concentration (tmax), and the plasma terminal half-life (t1/2).

To evaluate the safety and tolerability of treatment with single doses of a pellets based sachet formulation of esomeprazole in relation to a commercial tablet and a commercial capsule of esomeprazole by assessment of adverse events (AEs) and laboratory variables.

Study Design

The study was conducted as a single-centre, open-label, randomized, 3-way crossover bioequivalence study in which healthy male and female volunteers (referred to below as "subjects") received single doses of esomeprazole 40 mg, either as a pellets based sachet formulation, a commercial capsule, or a commercial tablet, under fasting conditions. Single oral doses of esomeprazole 40 mg were given either as a tablet, a capsule, or a pellets based sachet formulation. Batch numbers were: H 1365-01-03-08 for the tablet, H 1222-06-07-02 for the capsule, and H 1784-01-01-01 for the sachet formulation.

The pellets based sachet formulation was dispersed in 15 mL of water in a plastic cup prior to use. The suspension was administered orally. An additional 15 mL of water was used to suspend any esomeprazole granules remaining in the cup, and were administered orally to the subjects. Each subject was then given 170 mL of water to drink from a separate cup, in order to standardize the water intake after the different treatments. The investigational site was provided with disposable plastic cups (100 mL) and plastic spoons for preparation of the investigational product.

The capsules and tablets were administered orally with 200 mL of water. They were not to be divided, chewed, or crushed.

The subjects were instructed to fast (except for water) after 22.00 the evening before the study days. Water was allowed until 1 hour before drug administration.

A total of 96 healthy male and female subjects, aged between 20 and 50 years inclusively, with approximately 50% of each sex, were included in the study in order to have at least 88 evaluable healthy subjects completing the study. In total, 122 subjects were enrolled in this study. Ninety-six (96) subjects (40 males and 56 females) were planned for and randomized into the study. All 96 subjects completed the study. Two (2) subjects were excluded from the statistical PP analysis because of major protocol deviations. Ninety-four (94) of the randomized subjects were thus included in the statistical evaluation of the pharmacokinetic variables. All 96 randomized subjects were included in the safety analysis.

For the pharmacokinetic variables AUC, Cmax, and AUCt, a mixed model analysis of variance (ANOVA) with fixed effects for period, sequence, and treatment (sachet formulation, tablet, or capsule of esomeprazole) was used. The results were anti-logarithmized and 2-sided 90% CIs for the ratio of geometric means for the formulations (sachet/tablet and sachet/capsule) were calculated. The remaining secondary variables, t_{max} and $t_{1/2}$, are presented with descriptive statistics. A Per Protocol (PP) approach was used for the statistical analysis. Thus, data from subjects with major protocol deviations were excluded from the statistical evaluation. Subjects with pharmacokinetic data available from only 1 study day were also excluded from the statistical analysis and missing values were not replaced. Analyses and the evaluation of safety were done in the safety population, defined as all subjects who received at least 1 dose of randomized treatment with the investigational products and for whom post-dose data are available.

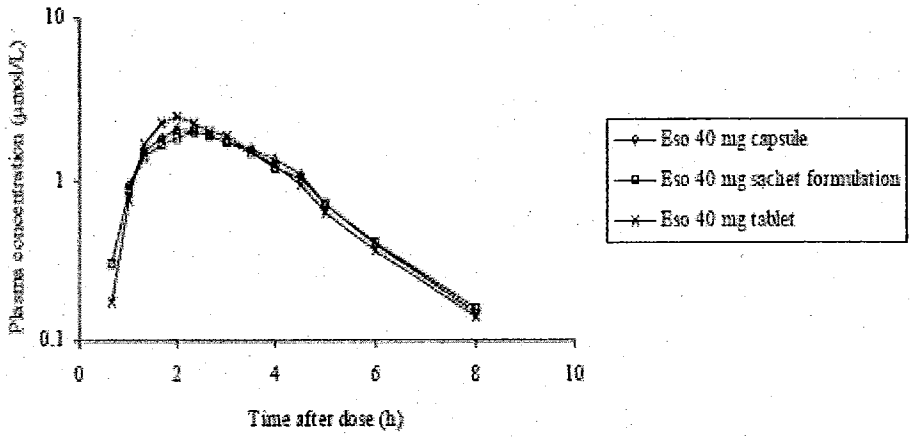
Drug concentration measurements

Samples for determination of esomeprazole in plasma were analyzed at [redacted] AstraZeneca R&D Mölndal, Sweden using validated normal-phase liquid chromatography and UV-detection according to method no. AS M-002 version 3 [redacted] implementation of AstraZeneca method no. BA-222). The limit of quantification (LOQ) of esomeprazole was 25 nmol/L.

Results

Though the sponsor conducted this study as a 3-arm crossover design with the proposed Sachet formulation, tablets and capsules, data pertaining to tablets are not reviewed here as esomeprazole tablets are not approved in the US. For the purpose of determining BE, data from sachet were reviewed against data from capsules only.

Mean plasma concentrations, log scale, of esomeprazole following single oral doses of 40 mg given as a sachet formulation, a tablet and a capsule in healthy male and female subjects under fasting conditions is shown in the following Figure.



The estimated geometric means and 95% CIs for AUC, Cmax, and AUCt for the sachet formulation, and the capsule of esomeprazole 40 mg, following single oral dosing, are presented in Table 1.

Table 1: Estimated geometric means of the pharmacokinetic variables in healthy male and female subjects under fasting conditions

Variable	Treatment	N	Estimate
AUC (µmol*h/L)	Sachet	94	5.85
	Capsule	94	5.97
Cmax (µmol/L)	Sachet	94	2.84
	Capsule	94	3.16
AUCt (µmol*h/L)	Sachet	94	5.73
	Capsule	94	5.85

The estimated ratios of the geometric means (sachet/tablet and sachet/capsule) and 90% CIs for AUC, Cmax, and AUCt following single oral doses of esomeprazole 40 mg, are presented in Table 2. The secondary variable AUCt has been listed together with the primary variables as this gives an additional comparison of the systemic exposure between the different formulations. As shown in Table 2, the 90% CIs for the ratios of the

geometric means (sachet/capsule) of AUC and Cmax were within the interval of 0.80 to 1.25, which is the stated criterion for bioequivalence. The 90% CIs for the ratios of the geometric means (sachet/capsule) of AUCt were also within the interval of 0.80 to 1.25. The mean of $t_{1/2}$ was approximately 1.1 hour and the median of tmax was 2.0 hours for both formulations (Table 2).

Table 2: Ratios (sachet/capsule) of geometric means and 90% CIs for AUC, Cmax and AUCt following single oral doses of esomeprazole 40 mg in healthy male and female subjects under fasting conditions

Variable	Treatment	N	GMR	90% CI	
				Lower	Upper
AUC(µmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03
C_{max}(µmol/L)	Sachet/Capsule	94	0.90	0.84	0.96
AUC_t(µmol*h/L)	Sachet/Capsule	94	0.98	0.93	1.03

Table 3: Descriptive statistics of t1/2 (h) and tmax (h) following single oral doses of esomeprazole 40 mg given as a sachet formulation, and a capsule in healthy male and female subjects under fasting conditions

Variable	N	Treatment	
		Sachet	Capsule
$t_{1/2}$ (h) ± SD	94	1.09 ± 0.46	1.07 ± 0.39
t_{max} (h) ± SD	94	2.32 ± 0.94	2.18 ± 1.01

Summary of safety results: According to the sponsor, all 3 formulations of esomeprazole were well tolerated in this study. There were no findings that raised any safety concerns. No trends of clinical importance were found regarding AEs in relation to the different formulations of investigational product. There were no pregnancies, no serious adverse events (SAEs), and no discontinuations of investigational product due to adverse events. No subject had a significant laboratory abnormality.

Conclusions
The 90% CIs for the ratios (sachet/capsule) of the geometric means for AUC, AUCt and Cmax were contained in the interval 0.80 to 1.25, and thus the new pellets based sachet formulation of esomeprazole is considered to be bioequivalent to the commercial capsule of esomeprazole 40 mg.

Esomeprazole 40 mg given as a sachet formulation resulted in similar values of tmax and $t_{1/2}$ as when given as a capsule.

All 3 formulations of esomeprazole were well tolerated in this study. There were no findings that raised any safety concerns.

Comment: *The reviewer's analysis of BE data between the sachet and capsule formulations are in agreement with the sponsor's result.*

4.3 Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-95	Brand Name	Nexium Delayed-Release Granules
OCP Division (I, II, III)	III	Generic Name	Esomeprazole magnesium
Medical Division	540	Drug Class	Proton Pum Inhibitor
OCPB Reviewer	Tapash K. Ghosh	Indication(s)	Acid-related disorder
OCPB Team Leader	Edward D. Bashaw	Dosage Form	Oral Sachets (20 mg, 40 mg)
		Dosing Regimen	1 sachet/day
Date of Submission	12/22/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/22/06	Sponsor	AstraZeneca
PDUFA Due Date	10/322/06	Priority Classification	3S
Division Due Date	8/15/06		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
eers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is the proposed product BE with the current approved capsule formulation?**	
Other comments or information not included above		
Primary reviewer Signature and Date	Tapash Ghosh	
Secondary reviewer Signature and Date	Dennis Bashaw	

CC: NDA 21- 957, HFD-850 (ELECTRONIC ENTRY OR LEE), HFD-170 (FURNESS), HFD-880 (TL, DD, DDD), CDR (B. MURPHY)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tapash Ghosh
10/5/2006 11:09:04 AM
BIOPHARMACEUTICS

Suliman Alfayoumi
10/5/2006 12:07:28 PM
BIOPHARMACEUTICS