A New Esomeprazole Packet (Sachet) Formulation for Suspension: In Vitro Characteristics and Comparative Pharmacokinetics Versus Intact Capsules/Tablets in Healthy Volunteers

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ABSTRACT

Background: A packet (sachet) formulation of esomeprazole for suspension has been developed for use in patients who have difficulty swallowing.

Objectives: This article reports the in vitro characteristics of the new esomeprazole formulation, including stability in suspension and suitability for administration orally or via enteral tubes. It also describes the pharmacokinetic profile of the esomeprazole 40-mg packet compared with that of existing solid dosage forms (capsules and tablets) in a clinical bioequivalence study.

Methods: The stability in suspension of the packet formulation was assessed after reconstitution at various strengths (2.5, 10, and 40 mg) and a different pH (3.4–5.0) in strength-appropriate volumes of water held at temperatures ranging from 5°C to 37°C for up to 60 minutes. Suitability for oral administration was examined in terms of reconstitution time and the actual dose delivered after simulated oral administration, as well as in terms of the actual dose delivered by enteral tubes ranging in diameter from 6 to 20 Fr. Chemical stability and suspension characteristics were also analyzed using alternative reconstitution vehicles (applesauce, apple juice, and orange juice). The comparative pharmacokinetics of the packet, capsule, and tablet formulations of esomeprazole were evaluated in a randomized, open-label, 3-way crossover study in healthy volunteers, who received single 40-mg doses of each formulation. Bioequivalence was assumed if the 90% CIs for the ratios of the geometric mean AUC and C_{max} were between 0.80 and 1.25. Reverse-phase liquid chromatography with ultraviolet detection was used to assess the esomeprazole content and/or degradation products of esomeprazole in the tests for in-suspension stability, dose delivery, and acid resistance. Normal-phase liquid chromatography was used to assess the esomeprazole content of the plasma samples in the bioequivalence study.

Results: At the pH and temperature ranges investigated, the packet formulation was stable for up to 60 minutes after reconstitution. Chemical degradation was low (<0.1%) for all reconstitution vehicles investigated. Reconstitution time was 2 minutes with water and 9 to 10 minutes with apple or orange juice. Dose delivery was ≥98% after simulated oral administration and was generally ≥96% after administration via enteral tubes. Ninety-six healthy volunteers (56 women, 40 men; mean age, 24.9 years; mean weight, 68.9 kg) participated in the randomized, crossover, comparative pharmacokinetic study of the packet and capsule/tablet formulations. The estimated ratios of the geometric mean AUC and C_{max} for the packet:capsule and packet:tablet formulations were 0.98 (90% CI, 0.93–1.03) and 0.99 (90% CI, 0.94–1.04), respectively.

Conclusions: In these analyses, the packet (sachet) formulation of esomeprazole was chemically stable in suspension and when administered orally and via enteral tubes. The formulation had a short reconstitution time, remaining fully dispersed in water for at

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least 30 minutes, and was dispersed in applesauce, apple juice, or orange juice without compromising its stability or dispersion characteristics. The packet formulation met the regulatory definition for bioequivalence to the tablet and capsule formulations. (*Clin Ther.* 2007;29:640–649)

Key words: esomeprazole packet, esomeprazole sachet, suspension stability, pharmacokinetics, bioequivalence, tube feeding, reconstitution.

INTRODUCTION

Proton pump inhibitors (PPIs) provide a high degree of gastric acid suppression and are the treatment of choice for patients with acid-related disorders such as gastroesophageal reflux disease and peptic ulcer disease.[1–4] These agents are most commonly available as orally administered solid dosage forms (ie, capsules or tablets). Some patient groups, however, including those with dysphagia, frail and elderly patients, and children, have difficulty swallowing. Therefore, alternative PPI dosing options have been explored,[5,6] including emptying the contents of capsule formulations into soft food or liquid before oral administration.[5–9]

A potentially more convenient method of oral administration is provided by packet (sachet) formulations, the contents of which are designed to be suspended in water (or a similar medium such as fruit juice) before consumption. A packet formulation of the PPI esomeprazole has been developed for use by patients who have difficulty swallowing. It can be administered orally by drinking, by enteral tube, or by syringe. The packet formulation contains acid-resistant esomeprazole pellets and excipient granules, and is designed to be reconstituted in water before use. Once reconstituted, the pellets are dispersed in a viscous suspension with a slightly citric taste. Different packet strengths (2.5, 5, 10, 20, and 40 mg) have been developed that are appropriate for use in patients of various ages and a range of clinical settings.

This report describes the in vitro characteristics of the esomeprazole packet formulation, including its in-suspension stability in water and its suitability for direct oral administration and administration via enteral tubes. Dispersion of the formulation in media other than water (eg, fruit juice, applesauce) was also investigated. Finally, a bioequivalence study was conducted in healthy volunteers to compare the pharmacokinetic properties of the esomeprazole packet formulation (40 mg) with those of commercially available esomeprazole capsule/tablet formulations of equivalent strength.

METHODS

For the purposes of the simulated oral administration experiments, the esomeprazole suspensions (20- and 40-mg strengths) were prepared according to the handling instructions in the US prescribing information for the delayed-release oral suspension of esomeprazole magnesium.[10] The contents of the 20- and 40-mg packets were mixed with 15 mL (1 Tbsp) water, stirred, left to thicken for 2 to 3 minutes, and then stirred again. The same handling procedures were applied to the 2.5-, 5-, and 10-mg packet strengths, except that the contents of the 2.5- and 5-mg packets were mixed with 5 mL (1 tsp) water.

All analyses, with the exception of the determination of plasma esomeprazole concentrations in the bioequivalence study, were performed at AstraZeneca R&D, Lund, Sweden.

Tests of Stability in Suspension and Reconstitution

The in-suspension stability of the reconstituted esomeprazole packet formulation was assessed at different dosage strengths (2.5, 10, and 40 mg) and a different pH (3.4–5.0) in strength-appropriate volumes of water held at temperatures ranging from 5°C to 37°C for up to 60 minutes. Chemical stability was also analyzed using applesauce, apple juice, and orange juice as reconstitution vehicles. In these experiments, the suspension was formed according to the handling instructions for a dosage strength of 40 mg in water[10] and was set aside for 30 minutes.

For all reconstitution vehicles, esomeprazole was assayed using isocratic reverse-phase liquid chromatography with ultraviolet (UV) detection at 302 nm. The liquid-chromatography column was a Zorbax Eclipse XDB C18 (5-μm particle size, 150 mm × 4.6 mm; Agilent Technologies, Santa Clara, California), and the mobile phase consisted of 35% acetonitrile in phosphate buffer (pH 7.3). Quantitation was performed against external standards. Degradation products of esomeprazole were assayed by gradient reverse-phase liquid chromatography with UV detection at 302 nm. The column was a Microspher C18 (3-μm particle size, 100 mm × 4.6 mm; Varian,

Walnut Creek, California). The gradient was obtained using 2 mobile-phase preparations; mobile phase A consisted of 10% acetonitrile in phosphate buffer (pH 7.6), and mobile phase B consisted of 80% acetonitrile in phosphate buffer (pH 7.6). Mobile phases A and B were mixed by the liquid chromatography pump as follows: 100% phase A for 1 minute, changed to 20% phase B over 10 minutes, changed to 100% phase B over 20 minutes, and finally held at 100% phase B for 1 minute. The total amount of degradation products was quantified relative to the total amount of esomeprazole in the formulation.

The test of reconstitution time was performed by adding the formulation to the specified amount of water or other reconstitution vehicle, and the time required for the esomeprazole pellets to become fully dispersed was determined. The standardized method of determining the actual reconstitution time involved first adding the full contents of a packet to a beaker containing the required volume of water (or alternative reconstitution vehicle). The suspension was immediately stirred for 15 seconds to distribute the esomeprazole pellets evenly and was then left to rest for 40 seconds, followed by stirring for 5 seconds. Next, the suspension was visually inspected for 30 seconds to determine whether the majority of the esomeprazole pellets were distributed in the suspension or were assembled at the bottom of the beaker. This procedure, with a 5-second stir and 30-second visual inspection, was repeated every minute. The reconstitution time was not measured when the reconstitution vehicle was applesauce, as the mixture was already viscous before addition of the formulation.

The in vitro dissolution test was based on the procedure described in the US Pharmacopoeia (USP) for delayed-release dosage forms[11]; that is, the drug product was first exposed to hydrochloric acid 0.1 mol/L for 2 hours, during which it was stirred at 100 rpm at 37°C using a USP apparatus 2. In vitro release at pH 6.8 was then determined. The amount of esomeprazole released after 30 minutes was analyzed by liquid chromatography, as outlined earlier.

Statistical Evaluation

Dissolution findings were evaluated using a reduced factorial design.[12,13] Multiple linear regression was used to fit a first-order polynomial, without interaction terms, as a model for the 11 experiments in the design. The 3 center points in the design were used to estimate the experimental error and thereby determine the statistical significance (95% CI) of the investigated factors (resting time and strength, pH and temperature of the suspension).

Dose Delivery and Acid Resistance After Simulated Administration

Analysis of the actual dose of esomeprazole delivered was performed after simulated administration (orally and via enteral tubes) of esomeprazole packet formulations corresponding to the 2.5- and 40-mg strengths. Tests of acid resistance (to evaluate the condition of the enteric coating of the esomeprazole pellets) were performed on the suspensions after their transit through enteral tubes. Acid resistance was also tested for the applesauce and fruit juice reconstitution vehicles, and was reported as a proportion of the added amount.

Direct Oral Delivery

After reconstitution of the esomeprazole packet formulation in an appropriate volume of water in a plastic cup, the cup was emptied in a standard manner that simulated drinking. A second equivalent amount of water was then added to the cup, which was emptied again. Finally, any esomeprazole pellets remaining in the cup were quantified to estimate the delivered dose.

Administration via Enteral Tubes

Five commercially available enteral tubes, ranging from 6 to 20 Fr in diameter and from 21 to 127 cm in length, were used for the simulated dose-delivery tests. These 5 tubes were an infant feeding tube (6 Fr, 105 cm; Pennine Healthcare, Derby, United Kingdom); a Dobhoff feeding tube (8 Fr, 109 cm; Kendall Health Care Products, Mansfield, Massachusetts); an Argyle Salem sump (14 Fr, 120 cm; Sherwood Medical, St. Louis, Missouri); a Levin tube (16 Fr, 127 cm; Medline Industries, Inc., Mundelein, Illinois); and a Bard trifunnel replacement gastrostomy tube (20 Fr, 21 cm; Bard Access Systems, Salt Lake City, Utah). Suspensions of esomeprazole 2.5 and 40 mg were prepared according to the handling instructions described earlier[10]; the appropriate volume of water and formulation was added to a standard commercially available polypropylene syringe (5 mL for the 2.5-mg strength and 15 mL for the 40-mg strength), after which the suspension was shaken and allowed to thicken. The suspension was then shaken and injected through the

enteral tube within 30 minutes. The syringe was refilled (with the same volume of water used initially) and shaken, and the remaining contents were flushed from the tube. Esomeprazole pellets flushed from the tubes were collected and analyzed by liquid chromatography to measure the esomeprazole content after passage through the tubes.

For each tube, 6 (2.5-mg strength) or 3 (40-mg strength) individual doses were fed through the tube into a USP 2 dissolution vessel containing hydrochloric acid 0.1 mol/L at 37°C stirred at 100 rpm. After 2 hours of acid exposure, the intact pellets were collected for assessment of acid resistance (esomeprazole assay by liquid chromatography).

Bioequivalence Study

A single-center, randomized, open-label, 3-way crossover study (study code: D9612C00032) was conducted in healthy adult volunteers to compare the pharmacokinetic properties of the packet formulation of esomeprazole (40 mg) with those of the same dose of commercially available esomeprazole tablets and capsules.* The protocol was approved by the Ethics Committee of Uppsala, Uppsala, Sweden. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised by the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000) and complied with international codes of good clinical practice. Informed consent was obtained from all volunteers before study participation.

Study Participants

Healthy male and nonpregnant, nonlactating female volunteers aged 20 to 50 years and with a body mass index between 19 and 27 kg/m^2 were eligible for participation. Childbearing potential was a cause for exclusion, unless the investigator considered that an individual understood the importance of avoiding pregnancy and of taking appropriate precautions against pregnancy (eg, intrauterine device, implantable progesterone device, oral contraceptive). The use of prescription medication, other than oral contraceptives, nasal sprays for nasal congestion, or acetaminophen (paracetamol) for temporary relief of pain, was not permitted during the study or in the 2 weeks before the first dose of study medication. No use of over-the-counter drugs, vitamins, or herbal or mineral products was permitted during the study or in the week before the first dose of study medication.

*Trademark: Nexium® (AstraZeneca, Mölndal, Sweden).

Drug Administration

On each of the 3 study days, which were separated by a washout period of at least 6 days, volunteers received esomeprazole 40 mg either as the packet formulation, tablet, or capsule. Volunteers were required to fast from 10 PM of the evening before each study day; water was allowed until 1 hour before drug administration. Standardized meals were provided on each study day.

The esomeprazole packet formulation was suspended in 15 mL water in a plastic cup and administered orally. An additional 15 mL water was then added and the contents ingested to ensure that any esomeprazole pellets remaining in the cup were administered. To standardize water intake after administration of the different treatments, each volunteer then drank another 170 mL water. The capsules and tablets were swallowed whole with 200 mL water.

Study Assessments

The primary objective of the study was to ascertain whether the esomeprazole packet formulation was bioequivalent to the commercially available tablet and capsule formulations. Bioequivalence was assessed based on total AUC and C_{max}. Secondary pharmacokinetic parameters of interest were AUC to the last quantifiable concentration (AUC_t), T_{max}, and $t_{1/2}$. For the determination of plasma esomeprazole concentrations, 5-mL blood samples were collected via an indwelling cannula in a forearm vein before dosing and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours after drug administration.

Samples for the determination of plasma esomeprazole concentrations were analyzed at Analytical Services, Quintiles AB, Uppsala, Sweden, using normal-phase liquid chromatography with UV detection at 302 nm. The column was a Superspher SI–Genesis Silica (4-µm particle size, 150 mm × 4.6 mm; Jones Chromatography Ltd., Cardiff, United Kingdom), and the mobile phase consisted of 1.4 mL ammonia solution 25%, 2 mL methanol, and 98 mL 2-propanol diluted to 1000 mL in dichloromethane (pH 6.5–7.0). Quantitation was performed against external standards. The limit of quantitation of esomeprazole was 25 nmol/L (interassay coefficient of variation <5%).

Drug tolerability was assessed based on adverse events reported spontaneously or elicited by direct questioning. Discontinuations due to adverse events and clinically important abnormalities in the results of routine laboratory tests (hematology, clinical chemistry, urinalysis) between screening and study end were also evaluated.

Statistical Evaluation

AUC, C_{max}, and AUC_t were logarithmically transformed and analyzed on a per-protocol basis. A mixed-model analysis of variance was used, with fixed factors for period, sequence, and treatment, and subject within sequence as a random effect. The results were antilogarithmized and expressed as estimates and 2-sided 95% CIs for the geometric means for each formulation, and estimates and 2-sided 90% CIs for the ratio of geometric means for each formulation (packet:capsule and packet:tablet). In accordance with standard regulatory requirements,[14] bioequivalence was assumed if the 90% CI for the ratios of the geometric means of the AUC and C_{max} fell within the interval from 0.80 to 1.25. The remaining pharmacokinetic variables and adverse events were presented descriptively.

The safety population was defined as all volunteers who received at least 1 dose of randomized treatment and for whom postdose data were available.

RESULTS

In-Suspension Stability and Reconstitution Tests

Across the ranges of parameters investigated (dosage strength, pH and temperature of the suspension, resting time after reconstitution), there was no significant effect on the stability of the esomeprazole packet formulation in suspension (**Table I**). The total amount of degradation products was <0.1% when water, applesauce, apple juice, and orange juice were used as reconstitution vehicles. Dissolution and dispersion of the esomeprazole pellets was maintained throughout the permitted resting time of 30 minutes during suspension in water (dissolution was not tested for the other reconstitution vehicles). At all dosage strengths investigated, the reconstitution time in water was 2 minutes. Using apple or orange juice as the reconstitution vehicles, the reconstitution time ranged from 9 to 10 minutes.

Dose Delivery and Acid Resistance After Simulated Administration

For both the 2.5- and 40-mg strengths of the packet formulation, the mean proportion of a dose delivered after simulated oral administration or transit through enteral tubes was generally ≥96% (the exceptions were 92% delivery of the 2.5-mg strength through the Argyle Salem sump and 89% delivery of the same strength through the Levin tube) (**Table II**). Acid resistance was high, with mean recovery of ~98% for the 2.5- and 40-mg strengths in water after simulated tube feeding (**Table III**); the results were similar for the 40-mg strength in orange juice, apple juice, and applesauce (**Table IV**).

Bioequivalence Study

Ninety-six volunteers (56 women, 40 men; mean [SD] age, 24.9 [5.6] years; age range, 20–50 years; mean weight, 68.9 kg; weight range, 54–92 kg) were randomized to treatment. With the exception of 1 Asian subject, all volunteers were white. Two volunteers were excluded from the bioequivalence analysis because of major protocol deviations. One of these subjects had a vasovagal reaction when the cannula was inserted in a forearm vein and was given a glass of juice; this was considered a major protocol deviation because the subject was not fasting at the time of drug intake. The second subject had nausea, vomiting, and stomach pain during study day 3. Vomiting started 2 hours and 40 minutes after drug intake, and the standard lunch required by the protocol could not be taken.

Pharmacokinetics

The plasma concentration–time profiles of esomeprazole were similar for the packet, tablet, and capsule formulations (**Figure**). The estimated geometric means and 95% CIs for the AUC, C_{max}, and AUC_t of esomeprazole 40 mg administered as the 3 formulations and the estimated ratios of the geometric means and 90% CIs are presented in **Table V**. Overall, the 90% CIs for the ratios of the geometric means of the AUC and C_{max} were within the interval from 0.80 to 1.25. For all 3 formulations, the mean $t_{1/2}$ was ~1.1 hours and the median T_{max} was 2 hours.

Tolerability

The most common drug-related adverse event was headache, which occurred in association with the packet, capsule, and tablet formulations in 10, 15, and 11 volunteers, respectively. There were no serious adverse events, discontinuations due to adverse events, or clinically important abnormalities in laboratory test results, vital signs, or electrocardiograms.

Table I. Stability of the esomeprazole packet formulation in water when the pH, temperature, and resting time of the suspension were varied.

Experiment No.	Strength, mg	pH of Suspension	Temperature of Suspension, °C	Resting Time After Reconstitution, min	Dissolution, % of Added Amount (n = 6) Mean (SD)	Range	Total Amount of Degradation Products, % of Esomeprazole
1	2.5	3.4	5	0	97 (1.3)	96–99	<0.1
2	2.5	5.0	5	60	95 (1.4)	94–97	<0.1
3	2.5	3.4	37	60	96 (3.4)	92–101	<0.1
4	2.5	5.0	37	0	98 (0.8)	97–99	<0.1
5	10	4.1	21	30	100 (0.7)	99–101	<0.1
6	10	4.1	21	30	98 (1.3)	96–100	<0.1
7	10	4.1	21	30	99 (0.5)	98–99	<0.1
8	40	3.4	5	60	98 (0.5)	97–98	<0.1
9	40	5.0	5	0	99 (0.3)	99–100	<0.1
10	40	3.4	37	0	98 (1.0)	98–100	<0.1
11	40	5.0	37	60	96 (1.0)	95–98	<0.1

Table II. Proportion of the dose delivered (% of added amount) after simulated oral or enteral-tube administration of the esomeprazole packet formulation reconstituted in water.*

	Esomeprazole 2.5 mg			Esomeprazole 40 mg		
Mode of Delivery	No. of Experiments	Mean (SD)	Range	No. of Experiments	Mean (SD)	Range
Oral	16	98 (1.9)	93–100	28	99 (0.5)	98–100
Enteral tube						
Infant feeding tube (6 Fr, 105 cm long)	6	96 (5.9)	85–102	6	100 (0.7)	99–101
Dobhoff feeding tube (8 Fr, 109 cm long)	6	97 (2.5)	93–100	6	100 (0.7)	99–101
Argyle Salem sump (14 Fr, 120 cm long)	6	92 (4.9)	83–97	6	101 (1.7)	99–104
Levin tube (16 Fr, 127 cm long)	6	89 (5.5)	81–95	6	100 (1.1)	98–101
Bard trifunnel replacement gastrostomy tube (20 Fr, 21 cm long)	6	96 (3.8)	90–100	6	99 (1.0)	98–101

*Values >100% are possible due to the precision of the experiments.

DISCUSSION

In the present investigation, studies of the stability of the esomeprazole packet formulation mixed with appropriate volumes of water indicated that the contents were fully dispersed within 2 minutes and, when administered orally or via a range of commercially available enteral tubes, delivered ≥96% of the dose in most cases. The esomeprazole pellets remained stable in the reconstituted suspension for up to 60 minutes, supporting the recommendation that the reconstituted

Table III. Mean acid resistance (% of added amount, corrected for corresponding dose delivered) of the esomeprazole packet formulation reconstituted in water after simulated administration via enteral tubes.*

Enteral Tube	Esomeprazole 2.5 mg (n = 6†)	Esomeprazole 40 mg (n = 3†)
Reference‡	99	99
Infant feeding tube (6 Fr, 105 cm long)	101	95
Dobhoff feeding tube (8 Fr, 109 cm long)	94	99
Argyle Salem sump (14 Fr, 120 cm long)	99	98
Levin tube (16 Fr, 127 cm long)	105	98
Bard trifunnel replacement gastrostomy tube (20 Fr, 21 cm long)	99	99

*Values >100% are possible due to the precision of the experiments.
†Number of times the simulated administration process was replicated for each type of enteral tube. For the purposes of analysis, the replicate administrations were pooled into 1 sample.
‡Suspensions not administered via enteral tubes.

Table IV. Mean acid resistance (% of added amount) of the esomeprazole packet formulation reconstituted in applesauce, apple juice, and orange juice (N = 3 experiments).*

Reconstitution Vehicle	Acid Resistance Mean (SD)	Range
Reference (water)	100 (0.3)	100–101
Applesauce	101 (0.7)	100–101
Apple juice	101 (0.1)	101–101
Orange juice	101 (0.4)	101–101

*Values >100% are possible due to the precision of the experiments.

product should be ingested within 30 minutes of preparation.[10] These results suggest that the esomeprazole packet formulation can be administered by several different modes, including orally, by enteral tubes, and by syringes, without compromise of its stability in suspension. Finally, the pharmacokinetic study in healthy adult volunteers found that after oral administration, a 40-mg dose of the esomeprazole packet formulation was bioequivalent to a 40-mg dose of the commercially available capsule and tablet formulations.

In the present study, the esomeprazole packet formulation had good stability (in terms of acid resistance), with complete recovery when emptied into small volumes of applesauce, orange juice, or apple juice, and a corresponding level of degradation products of <0.1%. This is consistent with the findings of an in vitro study of the stability of esomeprazole pellets from an opened, commercially available capsule suspended in various media,[8] in which esomeprazole pellets in orange or apple juice had >98% stability. The results of the present study indicated that the stability and dispersion characteristics of the esomeprazole packet formulation were not compromised when the contents were suspended in these vehicles (or in applesauce), although the bioequivalence of the formulation in these vehicles is yet to be established.

A similar high proportion of the dose was delivered after simulated oral administration across the dose range from 2.5 to 40 mg. The 40-mg dosage strength was chosen for investigation in the pharmacokinetic study because this is the highest available strength of the packet formulation. Overall, the 90% CIs for the ratios of the geometric mean esomeprazole AUC and C_{max} after administration of a single oral dose of the packet and capsule/tablet formulations satisfied the accepted regulatory criterion for bioequivalence.[14]

Given the small diameter of the esomeprazole pellets and the viscous suspension formed after reconstitution, the packet formulation was designed to prevent clogging within enteral tubes. For the 2.5- and 40-mg dosage strengths, suspension in a small volume of water (5 and 15 mL, respectively), followed by flushing with an equivalent volume, was found to be sufficient for complete transit of esomeprazole pellets from the packet formulation via a variety of small-caliber and standard nasogastric and gastric tubes, including tubes of diameters as small as 6 Fr. The packet formulation of lansoprazole, on the other hand, cannot be administered via enteral tubes because of

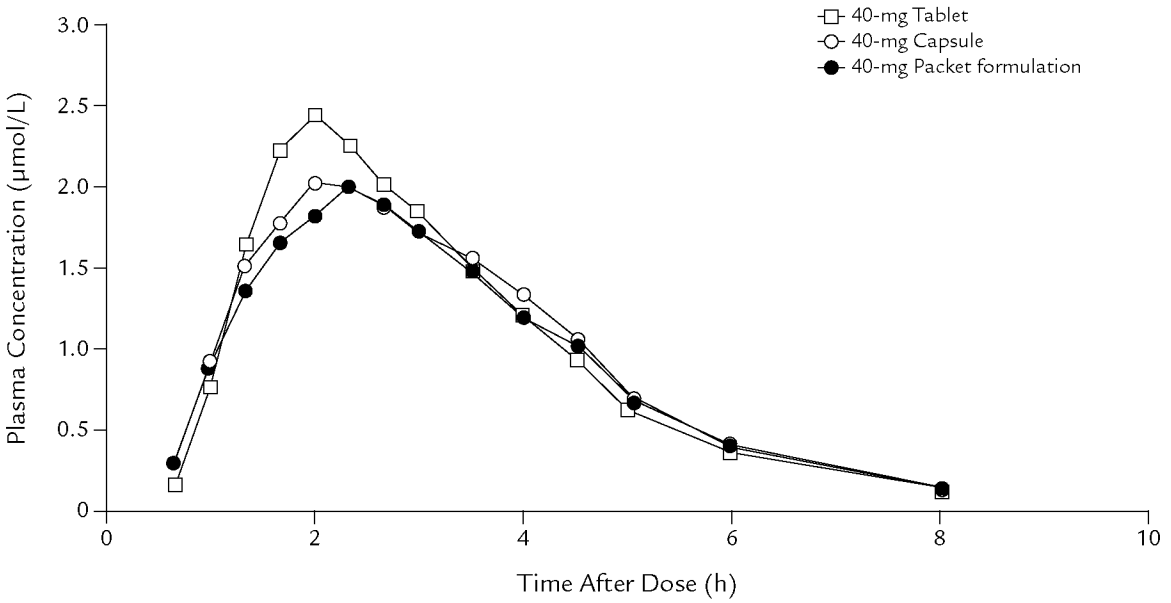

Figure. Mean plasma esomeprazole concentration–time profiles after administration of a single oral 40-mg dose given as the packet, capsule, and tablet formulations. From 8 hours onward, plasma levels were below the limit of quantitation for each formulation, and calculation of the means was not possible.

Table V. Estimated geometric means and ratios of the geometric means for AUC, C_{max}, and AUC_t in healthy adult volunteers (N = 94) administered single oral doses of esomeprazole 40 mg given as the packet, capsule, and tablet formulations.

	Geometric Mean (95% CI)			Ratio of Geometric Means (90% CI)	
Parameter	Packet	Capsule	Tablet	Packet:Capsule	Packet:Tablet
AUC, µmol · h/L	5.85 (5.00–6.85)	5.97 (5.10–6.99)	5.94 (5.08–6.95)	0.98 (0.93–1.03)	0.99 (0.94–1.04)
C_{max}, µmol/L	2.84 (2.51–3.21)	3.16 (2.79–3.57)	2.98 (2.64–3.37)	0.90 (0.84–0.96)	0.95 (0.89–1.01)
AUC_t, µmol · h/L	5.73 (4.90–6.70)	5.85 (5.01–6.85)	5.84 (4.99–6.83)	0.98 (0.93–1.03)	0.98 (0.93–1.03)
$t_{1/2}$, h*	1.09 (0.45–3.19)	1.07 (0.45–2.06)	1.06 (0.41–2.14)	ND	ND
T_{max}, h†	2.00 (1.00–5.00)	2.00 (0.67–4.53)	2.00 (1.00–6.00)	ND	ND

AUC_t = AUC to the last quantifiable concentration; ND = not determined.
*Values are arithmetic mean (range).
†Values are median (range).

rapid tube occlusion.[15] Moreover, based on the results of a search of MEDLINE for the past 5 years, the transit of the lansoprazole rapidly disintegrating tablet through enteral tubes has been tested only with tubes ≥8 Fr in diameter.[16]

The volume of water required for full delivery of a dose of the esomeprazole packet formulation through an enteral tube is relatively small (a maximum of 30 mL for a 40-mg dose, consisting of 15 mL for reconstitution and 15 mL for flushing). This is in contrast to the volume required when the contents of a PPI capsule are emptied into fluid and flushed down an enteral tube (eg, 80 mL in the study by Sostek et al[17]).

In general, the packet formulation of esomeprazole was well tolerated. Adverse events were as expected based on the clinical experience with esomeprazole.[18]

The packet formulation can be prepared quickly (<2 minutes) and remains fully dispersed for at least 30 minutes after reconstitution, without the need for continuous shaking. In contrast, when the contents of an esomeprazole capsule are added to an appropriate oral vehicle in a syringe, the syringe needs to be shaken gently and continuously throughout administration to ensure delivery.[17] Furthermore, the esomeprazole packet formulation remained dispersed and stable for as long as 30 minutes after preparation; in contrast, the lansoprazole packet formulation must be used immediately, and the rapidly disintegrating lansoprazole tablet needs to be administered within 15 minutes.[19]

CONCLUSIONS

In these analyses, the packet (sachet) formulation of esomeprazole was chemically stable in suspension and when administered orally and via enteral tubes. The formulation had a short reconstitution time, remaining fully dispersed in water for at least 30 minutes, and was dispersed in applesauce, apple juice, or orange juice without compromise to its stability or dispersion characteristics. The packet formulation met the regulatory definition for bioequivalence of the tablet and capsule formulations.

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