CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-456

20-973/S-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-456**	Submission Date(s): **1/9, 4/4, 5/9/02**
Brand Name	**Aciphex**
Generic Name	**Rabeprazole sodium**
Reviewer	**Jang-Ik Lee, Pharm.D., Ph.D.**
Team Leader	**Barbara Davit, Ph.D.**
OCPB Division	**DPE III (HFD-880)**
OND Division	**ODE IV DSPIDP (HFD-590)**
Sponsor	**Eisai, Inc.**
Relevant IND(s)	———
Submission Type; Code	**New indication, 6S**
Formulation; Strength(s)	**Tablet (delayed release), 20 mg**
Indication	***H. pylori* eradication**

1. EXECUTIVE SUMMARY

Rabeprazole, a substituted benzimidazole, is structually similar to omeprazole and lansoprazole, and reduces gastric acid secretion by proton pump inhibition. Since its approval in 1999 (N20-973), rabeprazole has been marketed in the United States under the trade name of Aciphex®, which is available as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. The approved indications of rabeprazole include healing and maintenance of healing of erosive or ulcerative gastroesophageal reflux disease, healing of duodenal ulcers, and treatment of pathological hyper-secretory conditions including Zollinger-Ellison syndrome. In this submission, the sponsor proposed an additional indication, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, for which rabeprazole is used in combination with amoxicillin and clarithromycin.

Dr. Joette Meyer was the initial Clinical Pharmacology and Biopharmaceutics (CPB) reviewer of this NDA for filing. Subsequently, this reviewer completed this CPB review. The information in this NDA is limited to the data to support the use of rabeprazole for *H. pylori* eradication. Other information is cross-referenced to the previously approved NDA (N20-973). Among the study reports submitted, a drug-drug interaction study conducted in the Netherlands (E-3810-E031-118) contains adequate information for labeling revision. Another drug interaction study conducted in Japan (E-3810-E031-201) was not reviewed in depth because a lower dose of clarithromycin and amoxicillin was used and because the overall conclusions were essentially the same as the study E-3810-E031-118. The sponsor also submitted a PK/PD study report (E3810-E044-402) without proposing any labeling revision based on the information in it. Upon the Agency's request, the sponsor provided a report demonstrating the dissolution performance of over-encapsulated products of amoxicillin, clarithromycin, and omeprazole used as the active

comparators in a pivotal clinical trial (E3810-A001-604) in comparison with corresponding regular products.

Statistically meaningful drug-drug interactions were observed in the study conducted in the Netherlands (E-3810-E031-118) following the combined administration of rabeprazole, clarithromycin, and amoxicillin. However, the magnitudes of the interactions are not expected to produce safety concerns. The over-encapsulated products of amoxicillin, clarithromycin, and omeprazole used in the trial E3810-A001-604 demonstrated virtually the same dissolution performance as compared with corresponding regular products.

1.1. Recommendation

According to the drug-drug interaction study conducted in the Netherlands (E-3810-E031-118), the exposure to rabeprazole and 14-hydroxyclarithromycin (the active metabolite of clarithromycin acknowledged as M5) following the triple combination therapy of rabeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg twice daily for 7 days was significantly greater than the exposure following each corresponding monotherapy. This finding needs to be incorporated into the rabeprazole labeling.

1.2. Phase IV Commitments

None

/S/

_____ Date: _____

Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacokinetics Reviewer
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/S/

_____ Date: _____

Barbara Davit, Ph.D.
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3. SUMMARY OF CPB FINDINGS

Pharmacokinetic interactions among rabeprazole, amoxicillin, and clarithromycin were evaluated in a four-way crossover study (E-3810-E031-118) with 16 healthy Caucasian male volunteers. All subjects were extensive metabolizers with respect to CYP2C19. Each subject orally ingested clarithromycin 500 mg alone, amoxicillin 1000 mg alone, rabeprazole 20 mg alone, or all together twice a day for 7 days. The pharmacokinetic parameters of each drug were determined following each 7-day treatment.

In a comparison of exposure to clarithromycin between test and reference treatments, mean maximum concentration (Cmax) and mean area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}) were virtually identical. For amoxicillin exposure, the geometric mean Cmax and AUC_{0-12} were not different between test and reference treatments because the 90% confidence intervals (90% CI) of their mean ratios were within the range of 80% - 125%. However, the geometric mean Cmax and AUC_{0-12} of clarithromycin metabolite M5 following test treatment were greater by 46% and 42%, respectively, than those following corresponding reference treatment. The geometric mean Cmax and AUC_{0-12} of rabeprazole following test treatment was greater by 34% and 11%, respectively than corresponding reference treatment. The respective 90% CIs were 104% - 141% and 90% -137%.

The statistically meaningful drug-drug interactions observed in this study are not expected to produce safety concerns. Considering that clarithromycin is not a drug of narrow therapeutic index and that the Cmax and AUC of its active metabolite M5 were only approximately one-third of the AUC of the parent compound, the contribution of the increase in the Cmax and AUC of M5 by 42% and 46%, respectively, to the overall safety of the triple combination therapy appears to be minimal. In comparison, an omeprazole-based combination therapy for *H. pylori* eradication was approved under the circumstances that the steady state mean Cmax, Cmin, and AUC_{0-8} of M5 were greater by 45%, 57%, and 45%, respectively, when clarithromycin 500 mg was given every 8 hours in combination with omeprazole 40 mg daily than when clarithromycin was administered alone. The increase in the Cmax and AUC_{0-12} of rabeprazole by 34% and 11%, respectively, is not a matter of safety concerns in the use of rabeprazole in combination with clarithromycin and amoxicillin. For comparison, a daily rabeprazole dose of 60 mg, which is three times larger than the dose administered in this study, has been approved in the treatment of Zollinger-Ellison syndrome.

The anti-secretory activity of rabeprazole 20 mg, omeprazole 20 mg, and lansoprazole 30 mg was determined by 24-hour pH monitoring before and after *H. pylori* eradication in healthy subjects (study E3810-E044-402). The anti-secretory drugs were administered once daily for 7 days. All anti-secretory drugs studied significantly inhibited the secretion of gastric acid both before and after *H. pylori* eradication, in comparison with placebo. In active treatments as well as placebo, intragastric acidity was generally higher after *H. pylori* eradication than beforehand. The difference between active treatment and placebo was not affected by *H. pylori* eradication. There were no consistently significant differences among the three anti-secretory drugs in their suppressive effect on gastric acid secretion.

To determine the equivalence between the over-encapsulated (for blinding purposes) active comparators of amoxicillin, clarithromycin, and omeprazole used in a pivotal clinical trial

(E3810-A001-604) and corresponding regular products, their dissolution performance was compared. Omeprazole showed no difference in dissolution performance between the over-encapsulated and corresponding regular capsules; similarity factors (f2) were within the range of 50 - 100 and the differences in % dissolution were less than 15% at all measured time points in 3 batches tested. In contrast, amoxicillin and clarithromycin demonstrated a minute difference in dissolution performance; although all f2 values were within the range of 50 - 100, % dissolutions were slightly greater than ——— at the first measurement point (—— min) in some batches tested. However, the dissolution performance is acceptable with respect to the dissolution requirements for amoxicillin capsules and clarithromycin tablets in United States Pharmacopoeia.

The plasma concentrations of rabeprazole, amoxicillin, clarithromycin, and clarithromycin metabolite M5 were measured by ———— In-process quality controls showed inter-assay precision (coefficient of variation) of 6.8% or lower, accuracy (deviation from nominal value) of 9.2% or lower, and reproducibility (mean difference between first and duplicate runs) of 11.2% or lower.

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4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Rabeprazole, a substituted benzimidazole, is structually similar to omeprazole and lansoprazole, and reduces gastric acid secretion by proton pump inhibition. Rabeprazole has been marketed under the trade name of Aciphex®, which is available as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. The information in this NDA is limited to the data to support the use of rabeprazole for *H. pylori* eradication. Other information is cross-referenced to the previously approved NDA (N20-973). Please see the reviews for N20-973 for detailed information regarding the physico-chemical properties and formulation of rabeprazole.

What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

Indication: Rabeprazole has been approved in 1999 for healing and maintenance of healing of erosive or ulcerative gastroesophageal reflux disease, healing of duodenal ulcers, and treatment of pathological hyper-secretory conditions including Zollinger-Ellison syndrome. In this submission, the sponsor proposed an additional indication of *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence. For this indication, rabeprazole is administered in combination with amoxicillin and clarithromycin.

Dosage and Route of Administration: For *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, the sponsor proposed an oral administration of rabeprazole 20 mg in combination with amoxicillin 1000 mg and clarithromycin 500 mg twice daily for 7 days.

Mechanism of Action: Rabeprazole, a benzimidazole proton pump inhibitor, undergoes an acid-catalyzed conversion to an active sulphenamide derivative which specifically inhibits H^+/K^+-ATPase activity on the surface of gastric parietal cells, thus blocking the final step in gastric acid secretion. Rabeprazole like other proton pump inhibitors have also been known to eradicate gastric *H. pylori* infection when administered in combination with antibiotics such as clarithromycin, amoxicillin, and metronidazole. A less acidic environment provided by rabeprazole appears to be favorable for the antibacterial drugs to kill the organism.

4.2. General Clinical Pharmacology

What biomarkers or pharmacodynamic parmeters were measured in clinical pharmacology studies? How are they used in the evaluation of the efficacy or safety of the drug studied?

The anti-secretory activity of rabeprazole 20 mg, omeprazole 20 mg, and lansoprazole 30 mg was determined before and after *H. pylori* eradication in a randomized, placebo-controlled, crossover study (E3810-E044-402). The anti-secretory drugs were administered once daily for 7 days. The *H. pylori* eradication was done by administration of ranitidine bismuth citrate 400 mg, tetracycline 500 mg, and clarithromycin 500 mg twice daily for 7 days. The PK/PD properties of

the anti-secretory drugs were assessed by monitoring of intragastric pH and measurement of plasma gastrin concentrations.

As shown in figure 1 and Table 1, all anti-secretory drugs studied significantly inhibited the secretion of gastric acid both before and after *H. pylori* eradication, in comparison with placebo by the mean area under the intragastric acidity-time curve using an analysis of variance (ANOVA). The comparison of the mean time of pH > 3 or 4 showed similar results.

Figure 1. Mean area under the intragastric acidity-time curve over the 24-hr period following once daily dose of antisecretary medications for 7 days (per-protocol analysis)

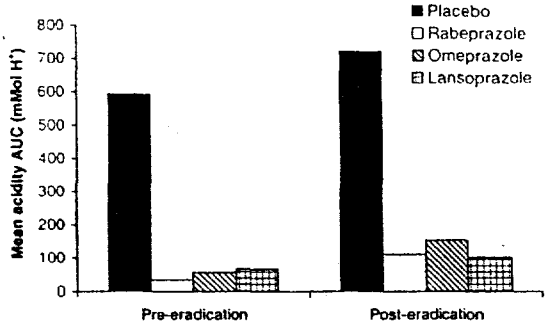
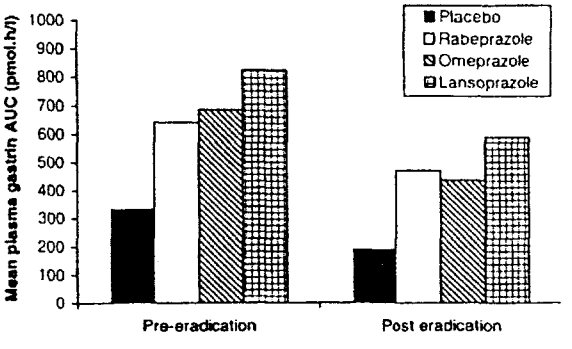


Table 1. Statistical significance of terms in an ANOVA model for the area under the intragastric acidity-time curve over the 24-hr period following once daily dose of anti-secretory medications for 7 days (per-protocol analysis)

Term	P value
Center	0.51
Treatment session	< 0.001
Period within treatment session	0.82
Treatment	< 0.001
Treatment x session interaction	0.54

In active treatments as well as placebo, intragastric acidity was generally higher after *H. pylori* eradication than beforehand, particularly at night. The change in gastric acid secretion after *H. pylori* eradication was more marked at nighttime than daytime. The difference between an active treatment and placebo was not affected by *H. pylori* eradication. This suggests that proton-pump inhibitors suppress acid secretion irrespective of *H. pylori* status. However, the anti-secretory drugs under *H. pylori* negative status do not reduce the intragastric acidity to such low levels as under *H. pylori* positive status because the levels started from a higher baseline in *H. pylori* negative status. There were no consistently significant differences among the three anti-secretory drugs studied in their suppressive effect on gastric acid secretion.

Figure 2. Mean area under the gastrin concentration-time curve over a period of 1800 - 1300 following once daily dose of antisecretary medications for 7 days



The area under the gastrin concentration-time curve were higher during anti-secretory treatment than during placebo treatment (Figure 2). For all treatments, post-eradication gastrin concentrations were lower than before eradication. The increase in plasma gastrin concentrations during anti-secretory treatment is known to be a normal physiological response to suppression of acid secretion, as the release of gastrin is stimulated by a lack of gastric acidity.

Overall, all 3 anti-secretory medications were clearly better than placebo in reducing gastric acidity. The relative comparison of anti-secretory efficacy between the 3 drugs studied showed no conclusive result. The anti-secretory effect of the 3 drugs studied were not reduced under *H. pylori* positive status as compared with that under negative status. The sponsor is not proposing any labeling revision based on these pharmacodynamic data.

4.3. Intrinsic Factors

The information for this section is cross-referenced to N20-973.

4.4. Extrinsic Factors

Did the exposure to clarithromycin and its metabolite M5 increase when clarithromycin was administered in combination with amoxicillin and rabeprazole as compared with when it was given alone?

Pharmacokinetic interactions among rabeprazole, amoxicillin, and clarithromycin were evaluated in a randomized, four-way crossover study (E-3810-E031-118) conducted in healthy volunteers in the Netherlands. A total of 16 Caucasians male subjects aged between 19 and 54 years old completed the study. Because CYP2C19 catalyzes a minor pathway of rabeprazole metabolism and could confound the result of this drug interaction study, subjects were genotyped with respect to CYP2C19 and turned out all extensive metabolizers. Each subject orally took clarithromycin 500 mg alone (Treatment A), amoxicillin 1000 mg alone (Treatment B), rabeprazole 20 mg alone (Treatment C), or all together (Treatment D) twice a day for 7 days. The drug doses were equivalent to current clinical doses in omeprazole-based triple therapy and the duration of dosing was the same as the anticipated duration for *H. Pylori* eradication. The pharmacokinetic parameters of the study drugs were determined after each 7-day treatment.

The exposure to clarithromycin metabolite M5 but not to the parent compound was increased when clarithromycin was administered in combination with amoxicillin and rabeprazole as compared with when it was given alone. Table 2 shows a summary of statistical analysis in the comparison of the pharmacokinetic parameters of clarithromycin and its metabolite M5 between test and reference treatments. The mean maximum concentration (Cmax), area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}), and terminal half-life ($t_{1/2}$) of clarithromycin were almost identical between test (Treatment D) and corresponding reference (Treatment A) treatments. The median time to Cmax (Tmax) of clarithromycin was longer following the test treatment. The geometric mean Cmax and AUC_{0-12} of M5 following test treatment were greater by 46% and 42%, respectively, than those following corresponding reference treatment. The median Tmax of M5 was longer in test treatment, whereas its mean $t_{1/2}$ was not different.

Table 2. Summary of statistical analysis in the comparison of the pharmacokinetic parameters of clarithromycin and clarithromycin metabolite M5 between test (Treatment D) and corresponding reference (Treatment A) treatments

Study Drug or Metabolite	Pharmacokinetic Parameter	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (%)	90% Confidence Interval (%)
Clarithromycin	Cmax (μg/mL)	3.26 ± 0.98	3.25 ± 0.87	100	87 - 114
	Cmin (μg/mL)	1.29 ± 4.4	0.93 ± 0.32		
	AUC_{0-12} (μg·hr/mL)	24.8 ± 7.9	24.0 ± 6.4	103	91 - 116
	Tmax (hr)*	2.5	1.5		
	$t_{1/2}$ (hr)	6.6 ± 1.0	6.6 ± 0.7		
Clarithromycin Metabolite (M5)	Cmax (μg/mL)	1.08 ± 0.23	0.74 ± 0.14	**146**	**133 - 160**
	Cmin (μg/mL)	0.61 ± 0.16	0.35 ± 0.13		
	AUC_{0-12} (μg·hr/mL)	9.77 ± 2.23	6.84 ± 1.39	**142**	**131 - 154**
	Tmax (hr)*	3.5	2.0		
	$t_{1/2}$ (hr)	11.0 ± 2.7	11.9 ± 3.5		

* median value

The exact reason for the increase in the mean Cmax and AUC_{0-12} of M5 following the triple combination therapy are not known. Considering that clarithromycin is not a drug of narrow therapeutic index and that the Cmax and AUC of its active metabolite M5 were only approximately one-third of the AUC of the parent compound, the contribution of the increase in the Cmax and AUC of M5 by 42% and 46%, respectively, without increasing the exposure to the parent compound, to the overall safety of clarithromycin use in combination with rabeprazole and amoxicillin appears to be minimal. By comparison, an omeprazole-based combination therapy for *H. pylori* eradication was approved under the circumstances that the steady state mean Cmax, Cmin, and AUC_{0-8} of M5 were greater by 45%, 57%, and 45%, respectively, and that the mean Cmax, Cmin, and AUC_{0-8} of clarithromycin were greater by 10%, 27%, and 15%, respectively, when clarithromycin 500 mg was given every 8 hours in combination with omeprazole 40 mg daily than when clarithromycin was administered alone.

Did the exposure to amoxicillin increase when amoxicillin was administered in combination with clarithromycin and rabeprazole as compared with when it was given alone?

The drug-drug interaction study E-3810-E031-118 demonstrated that the exposure to amoxicillin was not different when amoxicillin was administered in combination with clarithromycin and rabeprazole as compared with when it was given alone. Table 3 shows a summary of statistical analysis in the comparison of the pharmacokinetic parameters of amoxicillin between test and reference treatments. The geometric mean Cmax and AUC_{0-12} of amoxicillin were not different between the two treatments. The 90% confidence intervals (90% CI) for the geometric mean ratios of both Cmax and AUC_{0-12} of amoxicillin were within the range of 80% - 125%. The median Tmax of amoxicillin was slightly longer in test treatment. There was no effect on mean $t_{1/2}$.

Table 3. Summary of statistical analysis in the comparison of the pharmacokinetic parameters of amoxicillin between test (Treatment D) and corresponding reference (Treatment B) treatments

Study Drug	Pharmacokinetic Parameter	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (%)	90% Confidence Interval (%)
Amoxicillin	Cmax (μg/mL)	12.70 ± 2.67	11.58 ± 2.24	109	99 - 120
	Cmin (μg/mL)	0.69 ± 0.53	0.51 ± 0.84		
	AUC_{0-12} (μg·hr/mL)	38.8 ± 10.3	40.1 ± 7.8	95	90 - 101
	Tmax (hr)*	1.5	1.25		
	$t_{1/2}$ (hr)	1.2 ± 0.4	1.1 ± 0.2		

* median value

Did the exposure to rabeprazole increase when rabeprazole was administered in combination with clarithromycin and amoxicillin as compared with when it was given alone?

The drug-drug interaction study E-3810-E031-118 demonstrated that the exposure to rabeprazole was increased when rabeprazole was administered in combination with clarithromycin and amoxicillin as compared with when it was given alone. Table 4 shows a summary of statistical analysis in the comparison of the pharmacokinetic parameters of rabeprazole between test and reference treatments. The geometric mean Cmax and AUC_{0-12} of rabeprazole following test treatment (Treatment D) was larger by 34% (90% CI, 104% - 171%) and 11% (90% CI, 90 - 137%) than those following reference treatment (Treatment C). The mean $t_{1/2}$ of rabeprazole tended to be shorter with test treatment, while the median Tmax was not different. The Cmax and AUC_{0-12} of rabeprazole showed large inter-subject variation (coefficient of variation, 47% or larger).

Table 4. Summary of statistical analysis in the comparison of the pharmacokinetic parameters of rabeprazole between test (Treatment D) and corresponding reference (Treatment C) treatments

Study Drug	Pharmacokinetic Parameter	Test (Mean ± SD)	Reference (Mean ± SD)	Geometric Mean Ratio (%)	90% Confidence Interval (%)
Rabeprazole	Cmax (ng/mL)	387 ± 184	307 ± 185	**134**	**104 - 171**
	Cmin (ng/mL)	6.3 ± 13.0	16.3 ± 31.7		
	AUC_{0-12} (ng·hr/mL)	561 ± 264	516 ± 247	111	**90 - 137**
	Tmax (hr)*	3.0	3.0		
	$t_{1/2}$ (hr)	0.69 ± 0.15	0.79 ± 0.31		

* median value

The exact reason for the increase in the mean Cmax and AUC_{0-12} of rabeprazole following the triple combination therapy are not clearly known. It is suggested that clarithromycin increased the Cmax and AUC_{0-12} of rabeprazole by inhibiting CYP3A and/or CYP2C19. Both enzymes are involved in rabeprazole metabolism. The clinical consequence of this drug-drug interaction

is not known based on this study alone. However, the increases in the Cmax and AUC_{0-12} of rabeprazole by 34% and 11%, respectively, are not expected to produce safety concerns in the use of rabeprazole in combination with clarithromycin and amoxicillin. By comparison, a daily rabeprazole dose of 60 mg, which is three times larger than the dose administered in this study, has been approved in the treatment of Zollinger-Ellison syndrome.

An additional drug-drug interaction study (E-3810-E031-201) conducted in Japan was not reviewed in depth because a lower dose of clarithromycin (400 mg) and amoxicillin (750 mg) was administered and because its overall conclusions were essentially the same as conclusions in the study conducted in the Netherlands (E-3810-E031-118).

4.5. General Biopharmaceutics

Were over-encapsulated products used as active comparators in a pivotal clinical trial equivalent to corresponding regular products?

In a pivotal clinical trial (E3810-A001-604), the sponsor used over-encapsulated products of the active comparators of amoxicillin, clarithromycin and omeprazole for blinding purposes. Therefore, it is important to know whether the over-encapsulated products are equivalent to regular commercial products. Upon the request by the Agency, the sponsor provided the information regarding the dissolution performance of the over-encapsulated products in comparison with that of regular commercial products.

Amoxicillin: Commercial amoxicillin 500 mg capsules (Amoxil®, SmithKline Beecham) were over-encapsulated using — capsules sized — Dissolution performance was compared between the over-encapsulated and corresponding regular capsules. The sponsor submitted dissolution data obtained from two lots of amoxicillin capsules (0392 and KS1921). Dissolution conditions were as follows:

- Dissolution apparatus:	USP apparatus 2 (paddle)
- Dissolution media:	water, 900 mL
- Temperature:	37 ± 0.5 °C
- Rotation speed:	75 rpm
- Sampling time:	—, 60, — min
- Detection:	UV 272 nm
- Number of units tested:	12 (6 capsules x twice) capsules each

Figure 3 graphically illustrates representative dissolution profiles of the over-encapsulated and regular capsules of amoxicillin 500 mg and Table 5 displays a numeric summary of the comparison of their dissolution performance. Whereas Lot No. KS1921 showed no difference, Lot No. 0392 showed a minute difference in dissolution performance between the over-encapsulated and regular products. Although the similarity factor (f2) of 51.1 was within the similarity boundary of 50 to 100, the difference in % dissolution at 20 minute point (16.5%) was slightly greater than the cut-off value of 15% recommended by the Agency in the SUPAC (scale-up and postapproval changes) Guidance. The dissolution conditions and performance in this test met the requirements for amoxicillin capsules in current US Pharmacopoeia (Q = 80% within 60 min).

Figure 3. Representative dissolution profiles (N = 6 each) of the over-encapsulated (left panel) and regular capsules of amoxicillin 500 mg (Lot No. 0392, right panel).

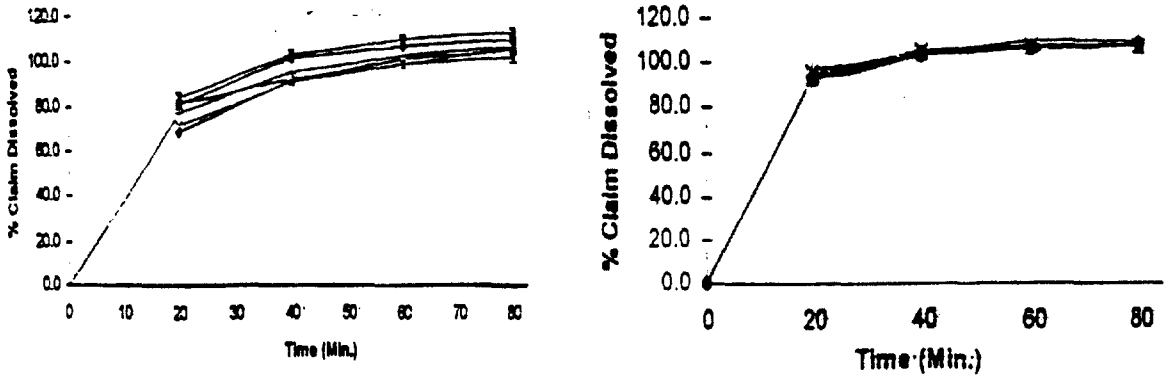


Table 5. Summary in the comparison of dissolution performance between the over-encapsulated and corresponding regular capsules of amoxicillin 500 mg (N = 12 each)

Dissolution Time (min)	Mean Dissolution (%)					
	Lot No. 0392			Lot No. KS1921		
	Over-Encapsulated	Regular	Difference	Over-Encapsulated	Regular	Difference
20	76.9	93.4	**16.5**	54.6	69.2	14.6
40	94.1	102.8	8.7	79.7	86.2	6.9
60	103.2	106.4	3.2	92.3	96.9	4.6
80	107.7	107.6	- 0.1	99.4	102.2	3.2
Similarity Factor (f2)	51.1			53.3		

Clarithromycin: Commercial clarithromycin 500 mg tablets (Biaxin®, Abbott laboratories) were over-encapsulated using — l capsules sized — Dissolution performance was compared between the over-encapsulated products and corresponding regular tablets. The sponsor provided dissolution data obtained from 3 lots (56-644-AA-21, 47-623-AA-21, and 47-633-AA-21). Lot No. 56-644-AA-21 was used in the clinical study, E3810-A001-604. Dissolution conditions were as follows:

- Dissolution apparatus: USP apparatus 2 (paddle) in a sink condition
- Dissolution media: 0.1 M acetate buffer (pH 5.0), 900 mL
- Temperature: 37 ± 0.5 °C
- Rotation speed: 50 ± 2 rpm
- Sampling time: 10, 20, 30, and 40 min
- Detection: —
- Number of units tested: 12 capsules or tablets (6 x twice) each

Figure 4 graphically illustrates representative dissolution profiles of the over-encapsulated capsules and commercial tablets of clarithromycin 500 mg, and Table 6 shows a numeric summary of the comparison of their dissolution performance. Whereas Lot Nos. 56-644-AA-21 and 47-623-AA-21 showed no difference, Lot No. 47-633-AA-21 showed a minute difference in dissolution performance between the over-encapsulated and regular products. Although the similarity factor (f2) of 52.5 was within the similarity boundary of 50 to 100, the difference in % dissolution at 10 minute point (17.6%) was slightly lager than the cut-off value of 15% recommended by the Agency in the SUPAC Guidance. The dissolution conditions and performance in this test met the requirements for clarithromycin tablets in current US Pharmacopoeia (Q = 80% within 30 min).

Figure 4. Representative dissolution profiles (N = 6 each) of the over-encapsulated products (Lot No. 14221DO, left panel) and corresponding regular tablets of clarithromycin 500 mg (Lot No. 56-644-AA-21, right panel).

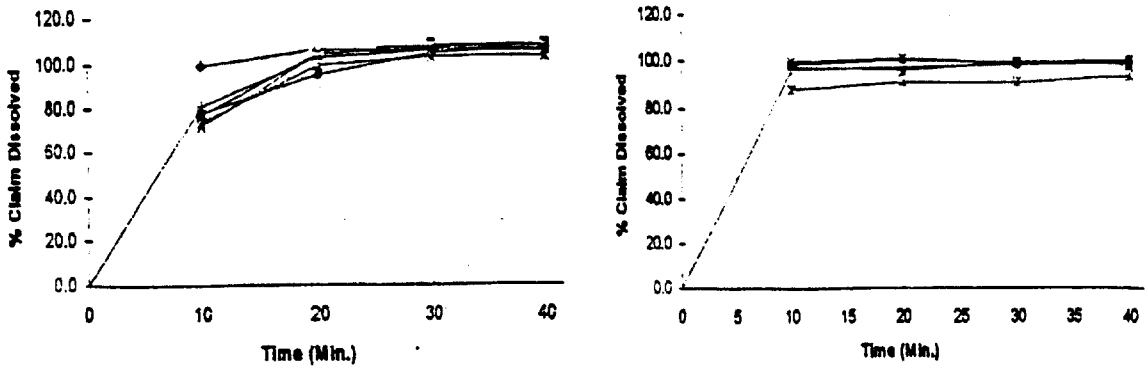


Table 6. Summary in the comparison of dissolution performance between the over-encapsulated products and regular tablets of clarithromycin 500 mg (N = 12 each)

Dissolution Time (min)	Mean Dissolution (%)								
	Lot No. 56-644-AA-21			Lot No. 47-623-AA-21			Lot No. 47-633-AA-21		
	Over-Encapsulated*	Regular	Difference	Over-Encapsulated**	Regular	Difference	Over-Encapsulated**	Regular	Difference
10	84.9	96.6	11.7	67.1	72.0	4.9	67.1	84.7	17.6
20	101.5	98.7	- 2.8	90.6	84.9	- 5.7	90.6	92.3	1.7
30	104.5	99.6	- 4.9	93.7	88.4	- 5.3	93.7	93.2	- 0.5
40	105.0	99.4	- 6.1	95.1	89.2	- 5.9	95.1	93.9	- 1.2
Similarity Factor (f2)	57.0			62.8			52.5		

* Lot No. 14221DO ** Mixed after over-encapsulation using Lot Nos. 47-623-AA-21 and 47-633-AA-21

Omeprazole: Commercial omeprazole 20 mg capsules (Prilosec®, AstraZeneca) were over-encapsulated using — capsules sized ~ Dissolution performance was compared between the over-encapsulated and corresponding regular capsules. The sponsor submitted dissolution data obtained from 3 lots (J2541, H5977, and H6285). Lot No. J2541 was used in the clinical study E3810-A001-604. Dissolution conditions were as follows:

- Dissolution apparatus: USP apparatus 2 (paddle)
- Dissolution media: 0.1 N hydrochloric acid 500 mL for 2 hours initially, then added 0.235 N phosphate buffer 400 mL (final pH 6.8 ± 0.5)
- Temperature:
- Rotation speed:
- Sampling time:
- Detection:
- Number of units tested:

Figure 5 graphically illustrates representative dissolution profiles of the over-encapsulated and commericial capsules of omeprazole 20 mg, and Table 7 shows a numeric summary of the comparison of their dissolution performance. The over-encapsulated capsules were not different from the regular capsules of omeprazole 20 mg in dissolution performance. The similarity factor (f2) in each comparison was within the range of 50 - 100 and the difference in % dissolution at each time point in each comparison was less than 15% recommended by the Agency.

Figure 5. Representative dissolution profiles (N = 6 each) of the over-encapsulated (Lot No. 14221CO, left panel) and regular capsules of omeprazole 20 mg (Lot No. J2451, right panel)

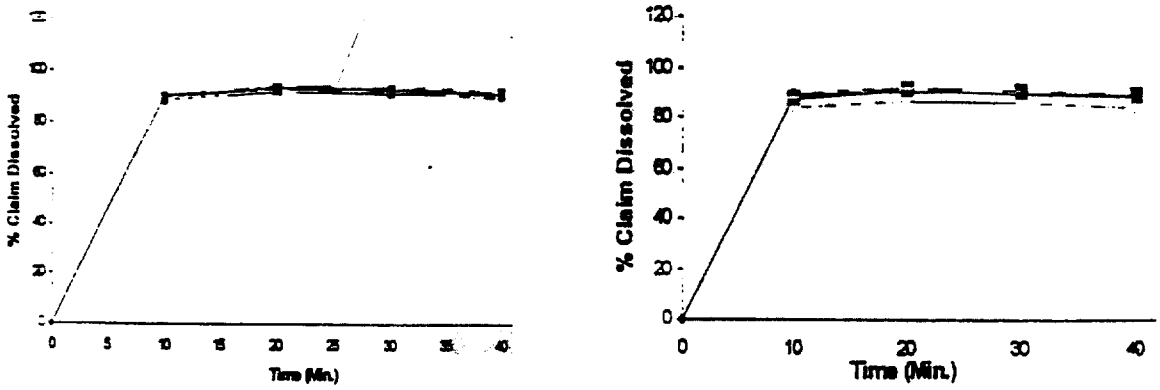


Table 7. Summary in the comparison of dissolution performance between over-encapsulated and regular capsules of omeprazole 20 mg (N = 12 each)

Dissolution Time (min)	Mean Dissolution (%)								
	Lot No. J2451			Lot No. H5977			Lot No. H6285		
	Over-Encapsulated*	Regular	Difference	Over-Encapsulated**	Regular	Difference	Over-Encapsulated**	Regular	Difference
10	90.2	88.0	- 2.2	92.0	92.0	0.0	92.0	90.0	- 2.0
20	93.7	91.0	- 2.7	93.8	92.3	- 1.5	93.8	90.0	- 3.8
30	93.0	90.5	- 2.5	92.6	91.2	- 1.4	92.6	89.7	- 2.9
40	91.5	89.3	- 2.2	91.5	90.6	- 0.9	91.5	88.7	- 2.8
Similarity Factor (f2)	82.0			91.2			75.4		

* Lot No. 14221CO ** Mixed after over-encapsulation using Lot Nos. H5977 and H6285

Overall, omeprazole showed no difference in dissolution performance between over-encapsulated and corresponding regular capsules. However, amoxicillin and clarithromycin demonstrated a minute difference in dissolution performance in comparison between over-encapsulated capsules and corresponding regular products. Both drugs showed slightly larger than 15% difference in % dissolution only at the first time point of measurement. This discrepancy is acceptable with respect to the dissolution requirements in United States Pharmacopoeia and not likely to produce a different clinical outcome.

4.6. Analytical

How were the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Which metabolites were selected for analysis and why?

Clarithromycin is a macrolide antibiotic drug with a broad spectrum of antibacterial activity. 14-Hydroxyclarithromycin (acknowledged as M5) has been identified as one of the major metabolites of clarithromycin. M5 has been shown to have substantial antimicrobial activity. After a typical dosing regimen (clarithromycin 500 mg twice daily), mean peak plasma

concentrations have been found to be in the order of 2 - 3 µg/mL for the parent drug and about 1 µg/mL for the metabolite. Therefore, the pharmacokinetic parameters of M5 were also compared between test and reference treatments in the drug-drug interaction study of E-3810-E031-118.

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/s/

Jang-Ik Lee
10/16/02 09:06:01 AM
BIOPHARMACEUTICS

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