

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-021

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
Review of Dissolution Specification

NDA: 22-021 Submission Date(s): January 29, 2007
Generic Name Ramipril
Reviewer Carol Noory
Team Leader Patrick Marroum
OCPB Division Division of Clinical Pharmacology I
ORM division Cardio-Renal Drug Products
Sponsor Cobalt Pharmaceuticals, Inc
Submission Type; Code request for change in dissolution specification
Formulation; Strength(s) 1.25 mg, 2.5 mg, 5 mg, 10 mg Tablet
Indication Treatment of Hypertension

Cobalt's current specification for dissolution testing of Ramipril tablet is _____
_____ On December 21, FDA requested that Cobalt apply a limit of: _____
_____ FDA also requested that Cobalt provide dissolution profiles and individual data for
stability batches from the original NDA as well as the recently submitted amendment to add an
additional source of API. On January 29, 2007, Cobalt responded to the request with the
dissolution profiles and individual data for the following products on stability:

Strength	Lot Number/Package	RT Stability Timepoint	Purpose of Batch
1.25 mg	F6034C – bottle of 30	6 months	Addition of API amendment
	D4001D – bottle of 30	Approx. 32 months	NDA Stability and Biobatch
2.5mg	F6035C – bottle of 30	6 months	Addition of API amendment
	D4002D – bottle of 30	Approx. 32 months	NDA Stability Batch
5 mg	F6036C – bottle of 30	6 months	Addition of API amendment
	D4003D – bottle of 30	Approx. 32 months	NDA Stability Batch
10 mg	F6037C – bottle of 30	6 months	Addition of API amendment
	D4004D – bottle of 30	Approx 32 months	NDA Stability and Biobatch

The following data was provided by the firm:

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/s/

Carol Noory
2/7/2007 12:08:07 PM
BIOPHARMACEUTICS

Patrick Marroum
2/7/2007 12:28:43 PM
BIOPHARMACEUTICS

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 22, 2006

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *CTV NOV 22, 06*
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 22-021, Ramipril
Tablets, Sponsored by Cobalt Pharmaceutical Inc.,
Mississauga, Ontario, Canada.

TO: Norman Stockbridge, M.D.
Director
Division of Cardio-Renal Products

At the request of the Division of Cardio-Renal Products (DCRP), the Division of Scientific Investigations (DSI) conducted an audit of the following bioequivalence studies:

Study Number: 2835

Study Title: "A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules in Normal Healthy Non-Smoking Male and Female Subjects for the USA"

Study Number: 2836

Study Title: "A Two-Way Crossover, Open-Label, Single-Dose, Fed, Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules in Normal Healthy Non-Smoking Male and Female Subjects for the USA"

data for these two subjects were reported, and all the plasma samples from subject 26 and 27 were re-analyzed for ramiprilat in a subsequent run. Since the LC/MS/MS method analyzed ramipilat and ramipril simultaneously, data for both analytes were available in the repeated run, although _____ only reported the ramiprilat data. However, at the request of the FDA investigator, _____ agreed to make available the original and repeat ramipril data (both generated from acceptable analytical runs) for audit. Similarly, 7 pharmacokinetic repeat plasma samples in Study 2835 and all plasma samples from subject 11 in Study 2970 also had original and repeat ramipril data from acceptable runs. These data are tabulated and provided in Attachment 2.

A comparison of the original and repeat ramipril data (see Attachment 2) shows that many plasma samples subjected to repeat analysis exhibited significantly different ramipril concentration data. This finding has raised questions regarding the accuracy of the reported rampril data. However, due to the small number of ramipril data available to evaluate incurred samples assay reproducibility [$<5\%$ (70/1388 subject samples) in Study 2835; $<1.3\%$ (18/1369 subject samples) in Study 2970], DSI is not able to confirm if there are significant assay reproducibility issues in other runs not cited in the Form FDA-483, Item 1.

Overall, DSI recommends that the ramipril data from subjects 26 and 27 in Study 2835 and subject 11 in Study 2970 (see Attachment 2) be excluded from bioequivalence determination. Additionally, for Study 2835, ramipril pharmacokinetic re-assay data from subject 14, period 2, 0.17 hr, and subject 31, period 2, 1, 1.25, and 1.5 hrs should also be discarded. The Review Division should consider requesting the sponsor to further address the incurred sample reproducibility issue for ramipril.

2. In Study 2970, 15 out of 29 subjects (subjects # 1, 4, 7, 8, 10, 12, 16, 17, 20, 22, 23, 26, 30, 31, 32) that completed the study exhibited significant ramiprilat concentrations ($>5\%$ C_{max} value) in the Study Period II pre-dose plasma samples. These significant carry-over results were not discussed in the final study report.

In each of the 15 subjects listed above, there was significant ramiprilat concentration ($> 5\%$ of C_{max} value)

in the pre-dose sample obtained in Study Period II. The OCPB reviewer should be aware of the significant ramiprilat carry over effect observed in these subjects, if the data of ramiprilat, an active metabolite of ramipril, are utilized to support bioequivalence determination between the test (Ramipril 1.25 mg Tablets) and reference products (Altace® 1.25 mg Capsules) in Study 2970.

3. Results from several failed validation studies (e.g., long term

_____ for ramipril and ramiprilat were discarded. The reasons for failure of these validation studies were not documented.

_____ acknowledged that their documentation for discarding failed validation data was not adequate.

_____ agreed to revise their SOP to assure that in the future every failed run during validation would be fully investigated and applicable corrective action documented.

During the inspection, the FDA investigator had reviewed data generated in the failed validation runs, and found that the cause for the failed validation runs was not due to the instability of the analytes, but rather due to errors from sample preparations.

Conclusion:

Following the inspection at _____ DSI recommends that:

1. Ramipril data from: (a) subjects 26 and 27 in Study 2835, (b) pharmacokinetic re-assay samples (subject 14, period 2, 0.17 hr; subject 31, period 2, 1, 1.25, 1.5 hrs) in Study 2835, and (c) subject 11 in Study 2970 should be excluded from bioequivalence determination. Additionally, the Review Division should consider requesting the sponsor to further address the incurred sample reproducibility issue for ramipril.
2. The OCPB reviewer should be aware of the significant ramiprilat carry over effect observed in the subjects cited in Form FDA-483 Item 2, if ramiprilat data are utilized to support bioequivalence determination between the test (Ramipril 1.25 mg Tablets) and reference products (Altace® 1.25 mg Capsules) in Study 2970.

After you have reviewed this memo, please append it to the original NDA submission.

Martin K. Yau
Martin K. Yau, Ph.D.

Final Classification:

cc:
HFA-224
HFD-45/rf
HFD-48/Yau/Himaya/cf
DCRP/Crowley
OCPB/DCPB1/Noory
HFR-NE200/Highgate Springs RP/Laplant
Draft: MKY 11/21/06
DSI:5695 O:\BE\eircover\22021bio.ram
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Amalia Himaya

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER New England District Office 1 Montvale Avenue Stoneham, MA 02180-3542 (781)596-7700	DATE(S) OF INSPECTION Oct. 30, 31, Nov. 1, 2, 3, 6, 2006
	FEI NUMBER _____

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: _____

FIRM NAME _____	STREET ADDRESS _____
CITY STATE AND ZIP CODE _____	TYPE OF ESTABLISHMENT INSPECTED _____

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1) Plasma samples subjected to repeat analysis exhibited significantly different ramipril concentration data.

For example:

In Study 2835 original and repeat ramipril data from acceptable analytical runs were available for all the plasma samples collected from subjects 26, 27 and 7 pharmacokinetic repeat plasma samples. _____ these plasma samples with measurable (>LOQ) ramipril concentrations exhibited _____ difference between the original and repeat data.

In study 2970, original and repeat ramipril data from acceptable runs were available for all the plasma samples collected from subject 11. _____ of these plasma samples with measurable (>LOQ) ramipril concentrations exhibited _____ differences between the original and repeat data.

2) In study 2970, 15 out of 29 subjects (subjects #1, 4, 7, 8,10, 12, 16, 17, 20, 22, 23, 26, 30, 31, 32) that completed the study exhibited significant ramiprilat concentrations (> 5% Cmax value) in the Study Period II pre-dose plasma samples. These significant carry-over results were not discussed in the final study report.

3) Results from several failed validation studies / _____ for ramipril and ramiprilat were discarded. The reasons for failure of these validation studies were not documented.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Martin K. Yau</i> <i>Paula Laplant</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Dr. Martin Yau, Pharmacologist Paula Laplant, Consumer Safety Officer	DATE ISSUED Nov. 6, 2006
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DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: March 23, 2006

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Carol Noory
Division of Clinical Pharmacology and Biopharmaceutics I
Office of Clinical Pharmacology and Biopharmaceutics

SUBJECT: Request for Biopharmaceutical Inspections
NDA 21-021 Ramipril Tablets

Study/Site Identification:

The following studies/sites pivotal to approval have been identified for inspection:

Study #	
2835	_____
2836	_____
2970	_____

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by June 31, 2006. We intend to issue an action letter on this application by July 31, 2006.

Should you require any additional information, please contact Alisea Sermon.

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Carol Noory
6/7/2006 11:07:42 AM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY
MEMO FOR FILE**

NDA: 22-021	Submission Date(s): January 9, 2006
Generic Name	Ramipril
Reviewer	Carol Noory
Team Leader	Patrick Marroum
OCPB Division	Division of Clinical Pharmacology I
ORM division	Cardio-Renal Drug Products
Sponsor	Cobalt Pharmaceuticals, Inc
Submission Type; Code	505(b)2
Formulation; Strength(s)	1.25 mg, 2.5 mg, 5 mg, 10 mg Tablet
Indication	Treatment of Hypertension

Re-evaluation of Study data

A DSI inspection of the study sites and the analytical site for Studies 2835 and 2970 was requested by the Office of Clinical Pharmacology. The data from these studies was deemed acceptable pending the outcome of the inspection. On November 22, 2006 the Division of Scientific Investigations made the following recommendations as a result of the inspection:

1. Ramipril data from: (a) subjects 26 and 27 in Study 2835, (b) pharmacokinetic re-assay samples (subject 14, period 2, 0.17 hr; subject 31, period 2, 1, 1.25, 1.5 hrs) in Study 2835, and (c) subject 11 in Study 2970 should be excluded from bioequivalence determination. Additionally, the Review Division should consider requesting the sponsor to further address the incurred sample reproducibility issue for ramipril.
2. The OCPB reviewer should be aware of the significant ramiprilat carry over effect observed in the subjects cited in Form FDA-483 Item 2, if ramiprilat data are utilized to support bioequivalence determination between the test (Ramipril 1.25 mg Tablets) and reference products (Altace® 1.25 mg Capsules) in Study 2970.

I recalculated the PK parameters eliminating the suggested subjects and the results are presented in the table below along with the original calculations:

Table 1: Study 2835 Original Pharmacokinetic Results				
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	16.77 ± 5.51	16.40 ± 5.285	236.67 ± 54.34	229.42 ± 61.68
AUC (0-inf) ng-hr/mL	17.30 ± 5.44**	17.40 ± 4.85*		
Cmax (ng/mL)	27.58 ± 9.16	25.11 ± 8.47	23.72 ± 2.00	23.23 ± 13.32
Tmax	0.50 ± (0.33-0.67)	0.50 (0.33-1.00)*	3.53 (1.00-6.00)*	2.00 (1.00-6.03)*
* n=29; ** n=28				
Table 2: Study 2835 Pharmacokinetic results without subjects 26 and 27				
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	16.44 ± 5.39	16.14 ± 5.19	238.47 ± 56.70	232.78 ± 62.65
AUC (0-inf) ng-hr/mL	16.93 ± 5.31*	17.27 ± 4.71**	319.38 ± 79.50	316.4 ± 86.43***
Cmax (ng/mL)	26.68 ± 8.6	25.56 ± 8.86	23.85 ± 13.20	23.65 ± 13.56
Tmax	0.45 (0.33-0.67)	0.55 (0.33-1.00)	2.19 (1.00-6.00)*	2.30 (1.00-6.03)*

n=27; * n=21; **n=18; ***n=26				
Table 3: Study 2970 Original Pharmacokinetic Results				
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	1.81 ± 0.93	1.75 ± 0.81	70.36 ± 20.73	74.81 ± 20.03
AUC (0-inf) ng-hr/mL	1.88 ± 0.96*	1.82 ± 0.86*	177.11 ± 97.10*	166.01 ± 52.83*
Cmax (ng/mL)	2.60 ± 1.20	2.50 ± 1.25	1.14 ± 0.48	1.16 ± 0.37
Tmax	0.50 (0.33-0.82)	0.53 (0.33-1.50)	3.50 (1.50-12.00)	3.25 (1.50-6.00)
* n=29; ** n=28				
Table 4: Study 2970 re-calculated Pharmacokinetic results (without subject 11)				
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	1.84 ± 0.94	1.77 ± 0.82	69.77 ± 19.14	73.98 ± 20.20
AUC (0-inf) ng-hr/mL	1.90 ± 0.97	1.84 ± 0.87*	171.25 ± 95.47**	163.18 ± 51.89***
Cmax (ng/mL)	2.67 ± 1.24	2.57 ± 1.33	1.08 ± 0.35	1.14 ± 0.36
Tmax	0.49 (0.33-0.82)	0.64 (0.33-1.50)	3.97 (2.00-12.00)	3.59 (1.50-6.00)
n=29; *n=28; **n=21; ***n=25				

The statistical results are presented in Table 5 for both the original calculations and the repeat calculations eliminating selected subjects.

TABLE 5: COMPARISON OF STATISTICAL OUTCOME FROM STUDIES 2538 AND 2790.				
Study 2835	90% CI			
Parameter	Original Calculations		Re-calculated results	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng-hr/mL	112.37% to 125.69%	100.59% to 107.52%	93.52% to 110.16%	97.40% to 109.52%
AUC (0-inf) ng-hr/mL	110.92% to 123.22%	94.67% to 107.13%	86.92% to 107.85%	95.04% to 108.18%
Cmax (ng/mL)	171.04% to 262.72%	106.27% to 128.39%	93.11% to 118.03%	90.88% to 116.22%
Study 2970				
Parameter	Original Calculations		Re-calculated results	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng-hr/mL	95.95% to 110.15%	87.61% to 99.34%	95.07% to 110.56%	87.40% to 99.33%
AUC (0-inf) ng-hr/mL	95.44% to 110.24%	89.50% to 120.20%	94.62% to 110.64%	88.83% to 121.24%
Cmax (ng/mL)	96.65% to 116.30%	90.87% to 102.93%	96.02% to 117.90%	90.21% to 101.27%

The information for ramipril was used to determine bioequivalence. Ramiprilat data was used to support the bioequivalence determination. The recalculated data did not include any pharmacokinetic repeat assays.

Recommendations

The recalculations eliminating subjects recommended by DSI did not impact the determination of bioequivalence. The studies have shown that the products are bioequivalent and the recommendations remain the same.

Signatures

Reviewer: _____

Team Leader Concurrence _____

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Carol Noory
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Patrick Marroum
2/1/2007 03:18:05 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
Review of an Amendment

NDA: 22-021	Submission Date(s): November 17, 2006
Generic Name	Ramipril
Reviewer	Carol Noory
Team Leader	Patrick Marroum
OCPB Division	Division of Clinical Pharmacology I
ORM division	Cardio-Renal Drug Products
Sponsor	Cobalt Pharmaceuticals, Inc
Submission Type; Code formulation	Amendment-new drug substance and addition of color to
Formulation; Strength(s)	1.25 mg, 2.5 mg, 5 mg, 10 mg Tablet
Indication	Treatment of Hypertension

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1. EXECUTIVE SUMMARY

This NDA is currently under review. The Office of Clinical Pharmacology has found the original submission to be acceptable with the exception of the specification for the dissolution procedure. The sponsor's proposed dissolution specification, Q _____ is not acceptable. The following dissolution method and specification is recommended based on the data evaluated.

USP Apparatus 2:	Paddle Method
Rotation speed:	50 rpm
Volume:	500 mL
Medium:	0.1 N HCl
Tolerance:	Q = _____

In the current amendment, the firm has requested approval of an additional supplier of the active pharmaceutical ingredient (API) and modification to the original formulation to allow for adding pharmaceutical dyes to identify the tablets. The tablets will be manufactured for King Pharmaceutical by Arrow Pharm (Malta) Ltd., Birzebbugja Malta. The original API was manufactured by _____ The new submission requests approval of _____ as an API supplier. The _____ ramipril has a different particle size than the _____ API which was tested in vivo. The 2.5-mg, 5-mg and 10-

mg tablets were further modified by adding pharmaceutical grade dyes to the formulation to aid in the identification of the different strengths of the product. _____
_____ account for the added color components. The 1.25 mg formulation is not being changed.

For some new drug substances intended for use in solid drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In this case, dissolution tests were performed comparing the exhibition batches made with the new drug supplier and color additives to the original 10 mg biolot (D4004) made with the _____ API and no color additives using the proposed dissolution method above.

COMMENTS

- The dissolution method is acceptable, the specification should be changed to Q= _____ based on the data provided for both the new formulation using the _____ API and the _____ API.

1.1 RECOMMENDATIONS

The supplemental development work has confirmed that the use of an alternate API source and addition of color does not impact the dissolution profiles of the drug product. The request for approval of _____ as an additional supplier of the active pharmaceutical ingredient (API) and modification to the original formulation to allow for adding pharmaceutical dyes to identify the tablets is acceptable. The firm should provide comparative solubility data for both the _____ and the _____ ramipril API in aqueous media from pH 1.2 to 7.5. The dissolution method is acceptable, the specification should be changed to Q= _____ based on the data provided for the new formulation using both the _____ API and the _____ API. The labeling should be changed to eliminate the reference in the Clinical Pharmacology portion of the labeling under "Pharmacokinetics and Metabolism" which begins "In trials in which subjects....." The changes are shown in section 3.0 of the review. The Recommendations (Section 1.1) should be forwarded to the firm

Signatures

Reviewer: _____

Team Leader Concurrence _____

cc list: NDA 22-021; HFD-860: (Noory, Mehta); HFD-110

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Carol Noory
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Patrick Marroum
1/18/2007 01:58:18 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-021 Submission Date(s): January 9, 2006
Generic Name Ramipril
Reviewer Carol Noory
Team Leader Patrick Marroum
OCPB Division Division of Clinical Pharmacology I
ORM division Cardio-Renal Drug Products
Sponsor Cobalt Pharmaceuticals, Inc
Submission Type; Code 505(b)2
Formulation; Strength(s) 1.25 mg, 2.5 mg, 5 mg, 10 mg Tablet
Indication Treatment of Hypertension

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1. EXECUTIVE SUMMARY

Cobalt Pharmaceuticals has developed a ramipril tablet that provides a pharmaceutical alternative to the reference listed drug, Altace® immediate-release capsules. The sponsor proposes to

market the tablets in strengths of 1.25 mg, 2.5 mg, 5 mg, and 10 mg which are formulated to be bioequivalent to Altace® (NDA 019901) which is manufactured by King Pharmaceuticals Inc.

This application includes no clinical trials; however, the bioequivalence and clinical safety of Ramipril tablets were investigated in a single-dose in vivo study conducted in healthy subjects comparing the 10 mg ramipril tablet to a 10 mg Altace® capsule under fasting conditions. The sponsor also compared the lowest strength, 1.25 mg ramipril tablet to the 1.25 mg Altace® capsules. A food-effect study was conducted to determine the effect of food on Ramipril tablets compared to Altace® capsules using the 10 mg product. The firm used a suitable dissolution procedure for the ramipril tablet. Dissolution profiles were evaluated for 1.25 mg, 2.5 mg, 5 mg, and 10 mg tablets compared to the corresponding strength of Altace® capsules using the proposed dissolution method to support a biowaiver for the 2.5-mg and 5-mg strength tablets. Literature was submitted to indicate that the kinetics of ramipril increases with increased dose, but is not strictly dose-proportional. The 24-hour AUC for ramiprilat is dose-proportional over the 2.5-20 mg dose range. The sponsor is relying on the Agency's findings of safety and efficacy for Altace® Capsules, USP, originally approved in 1991.

The clinical pharmacology and biopharmaceutics section of this application is acceptable based on the following:

1. The firm has demonstrated that the highest proposed strength (10 mg) of ramipril tablet was bioequivalent to the approved 10-mg Altace® reference product manufactured by King Pharmaceuticals.
2. The firm has also demonstrated that the lowest proposed strength (1.25 mg) of ramipril tablet was bioequivalent to the approved 1.25-mg Altace® reference product manufactured by King Pharmaceuticals.
3. A food effect study was conducted comparing the effect of food on the bioavailability of ramipril tablet to Altace® capsule using the 10 mg product.
4. A waiver for the middle two strengths, 2.5-mg and 5.0-mg tablet, was requested and found acceptable based on formulation proportionality and similarity of the dissolution profiles comparing each strength to the 10-mg Ramipril biot and to the Altace® capsules using a single dissolution procedure.
5. The sponsor evaluated a single dissolution method for this product. The dissolution method was originally developed for the sponsor's ANDA ramipril capsules and is the uses the same apparatus and medium as the approved method for Altace capsules. The proposed labeling is acceptable.
6. A DSI inspection of the study sites and the analytical site has been requested and is pending. The data from these studies is deemed acceptable pending the outcome of the inspection.

COMMENTS:

The sponsor's proposed dissolution method is acceptable. After evaluation of all of the dissolution data submitted, it appears that the ramipril tablets can meet a tighter specification. The agency recommended dissolution procedure, based on the data submitted, is the Paddle apparatus, 50 rpm with 500 mL of 0.1 N HCL as the medium. The Q value should be _____

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 22-021 and finds the clinical pharmacology and biopharmaceutics section acceptable. A waiver for the middle two strengths, 2.5-mg and 5.0-mg tablet, was requested and found acceptable based on formulation

proportionality and similarity of the dissolution profiles using a single dissolution procedure to compare each strength to the 10-mg Ramipril lot used in the *in vivo* studies. The sponsor's proposed dissolution specification, Q _____ is not acceptable. The following dissolution method and specification is recommended based on the data evaluated.

USP Apparatus 2:	Paddle Method
Rotation speed:	50 rpm
Volume:	500 mL
Medium:	0.1 N HCl
Tolerance:	Q = _____

1.2 PHASE IV COMMITMENTS

There were no Phase IV commitments.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Ramipril is a second generation, nonsulfhydryl-containing angiotensin converting enzyme (ACE) inhibitor approved for oral administration and marketed by King Pharmaceutical under the brand name Altace®. Ramipril is indicated for the treatment of hypertension.

1. Cobalt Pharmaceuticals has developed a new tablet dosage form of ramipril that provides a pharmaceutical alternative to the currently approved capsule formulation. Cobalt Pharmaceuticals proposes to market the tablets in 1.25-mg, 2.5-mg, 5-mg, and 10 mg strengths, which are formulated to be bioequivalent to Altace® Capsules manufactured by King Pharmaceuticals.

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 Altace® Capsules, USP (NDA 019901), originally approved in 1991. The submission contains the following information supporting approval of the NDA:

A. BIOEQUIVALENCE STUDIES

- a. Study 2835: A Two-Way Crossover, Open-label, Single-dose, Fasting Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules in Normal Healthy Non-smoking Male and Female Subjects for the USA.
 - i. **Ramipril-Study 2835:** Based on the statistical results for ramipril, the 90% confidence intervals of the relative mean for AUC_{0-t}, AUC_{0-inf} and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%.
 1. The 90% confidence intervals of the geometric means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were [94.81-109.35%], [89.12-106.25%], and [97.97-122.04%], respectively.
 2. The ratio of geometric means was 1.0 for AUC(0-t); 1.0 for AUC(0-inf) and 1.1 for C_{max}
 3. There was no significant difference in the *k_{el}* and *t* _{1/2} values between treatments (*p*>0.05) for ramipril. The total exposure to ramipril was similar between the two treatments.

4. The intra-subject variation for ramipril ranged from 14.6% to 24.82%.
- ii. **Ramiprilat-Study 2835:** Based on the statistical results for ramiprilat, the 90% confidence intervals of the relative mean for AUC_{0-t} and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%.
 1. The 90% confidence intervals for AUC_{0-t} and C_{max} were [98.04-109.78] and [91.56-116.03%], respectively. Due to the long elimination half-life of ramiprilat, the percentage of extrapolation for AUC_{0-inf} was greater than 20% for many subjects, and the average ratio of AUC_{0-t} to AUC_{0-inf} was approximately 74%. Therefore, the results of AUC_{0-inf} were not used for assessment of bioequivalence.
 2. The ratio of geometric means was 1.0 for AUC(0-t) and 1.0 for C_{max}.
 3. There was no significant difference in the k_{el} and t_{1/2} values between treatments (p>0.05) for ramiprilat.
 4. The intra-subject variations for all parameters for ramiprilat were between 12.64% and 26.45%.
 - iii. **Safety Study-2835:** There were no serious adverse events reported. No significant safety concerns were raised.
- b. Study 2836: A Two-Way Crossover, Open-label, Single-dose, Fed Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules in Normal Healthy Non-smoking Male and Female Subjects for the USA
- i. **Ramipril:** The 90% CI for the AUC_{0-t} and C_{max} of the test compared to the reference formulation was found not to be within the range of 80% -125%. This post-prandial bumping of the peak concentrations of the parent compound was associated with a significant delay in ramipril absorption from the reference capsules, as compared to absorption under fasted conditions (Study 2835). Based on the statistical results for ramipril, the 90% confidence intervals of the relative mean for AUC_{0-inf} was within 80% to 125%.
 1. The 90% confidence intervals for AUC_{0-t} and C_{max} were [112.37-125.69] and [171.04-262.72%], respectively. The 90% CI for AUC_{0-inf} was 110.92-123.22%.
 2. The geometric means ratio for the AUC_{0-t}, C_{max} and AUC_{0-inf} were 1.2, 2.1 and 1.2 respectively.
 3. The intra-subject variation was high for C_{max} [48.86%].
 4. T_{max} was 0.99 hours for ramipril and 2.39 hours for Altace capsules. A delay in the absorption of ramipril as a result of the co-administration of food is described in the reference product information.
 5. There was no significant difference in the k_{el} and t_{1/2} values between treatments (p>0.05) for ramipril.
 - ii. **Ramiprilat:** Based on the statistical results for ramipril, the 90% confidence intervals of the relative mean for AUC_{0-t} and AUC_{0-inf} was within 80% to 125%. The 90% confidence interval for C_{max} was not within 80-125%.

1. The 90% confidence intervals for C_{max} was [106.27-128.39%], slightly above the upper level to determine bioequivalence. The geometric means ratio for C_{max} was 1.2. The intra-subject variation for C_{max} was 21.53%.
 2. The 90% confidence intervals for AUC_{0-t} and AUC_{0-inf} were [100.59-107.52%] and [94.67-107.13%], respectively. The geometric means ratio for AUC_{0-t} and AUC_{0-inf} were 1.0 and 1.0 respectively.
 3. There was not significant difference between t_{1/2} and Kel.
- iii. **Safety:** There were no serious adverse events reported. There were a total of ten AEs reported by 8 subjects during the study and two subjects withdrew due to AEs. The relationship to the study drug was considered "possible" responsible for one of the AEs. One subject was lost to follow-up; one subject had an AE that is ongoing, all other subjects recovered completely from their AEs. No significant safety concerns were raised.
- c. Study 2970: A Two-Way Crossover, Open-label, Single-dose, Fasting Bioequivalence Study of Ramipril 1.25 mg Tablets Versus Altace® 1.25 mg Capsules in Normal Healthy Non-smoking Male and Female Subjects for the USA
- i. **Ramipril:** Based on the statistical results of ramipril, the 90% confidence intervals of the relative mean for AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%.
 1. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} were (95.95-110.15%), [95.44-110.24%], and [96.65-116.30%], respectively.
 2. The statistical results indicate that the geometric means ratio AUC_{0-t}, AUC_{0-inf}, and C_{max} were 1.0, 1.0 and 1.1, respectively.
 3. There was no significant difference in the kel and t_{1/2} values between treatments (p>0.05) for ramipril.
 - ii. **Ramiprilat:** Based on the statistical results of ramiprilat, the 90% confidence intervals of the relative mean for AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%.
 1. The 90% confidence intervals of the geometric means ratio for AUC_{0-t}, AUC_{0-inf}, and C_{max} were (87.61-99.34%), [89.50-120.20%], and [90.87-102.93%], respectively.
 2. The statistical results indicate that the ratio of geometric means for AUC_{0-t}, AUC_{0-inf}, and C_{max} ratio of were 0.93, 1.0 and 1.1, respectively.
 3. There was no significant difference in the kel and t_{1/2} values between treatments (p>0.05) for ramiprilat.
 4. The intra-subject variation for C_{max} of ramipril is significantly elevated.
 - iii. **Safety:** No serious AEs were reported and no subjects discontinued the study due to AEs. No significant safety concerns were raised.

B. LITERATURE STUDY

The Ramipril 505(b)(2) NDA clinical information is supported by way of reference to the approved NDA for Altace™ (N-019901) and certain pertinent literature regarding the use of ramipril in the treatment of hypertension. Fifty-three references were cited. A summary of the literature study submitted is given in Appendix 4.3.

C. WAIVER REQUEST

A biowaiver was requested for the two middle strengths, 2.5-mg and 5.0-mg tablets, based on formulation proportionality and the in vitro dissolution f2 comparison, which were similar using the dissolution procedure selected. This waiver is acceptable based on criteria stated in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations". This guidance states that "when the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients, an in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and an in vivo study on the highest strength."

D. DISSOLUTION STUDIES

- a. An in vitro evaluation of the currently approved dissolution procedure for Altace™ capsules (with the exception of the paddle speed) demonstrated that this method was acceptable for the Ramipril tablet. The method approved for Altace™ capsules is the USP Paddle method, 75 rpm with 500 mL of 0.1N HCl as the medium. The method proposed for ramipril tablets consists of:
USP Apparatus II, Paddle Method, 50 rpm
500 mL of 0.1N HCl
- b. The dissolution method was also used to compare the 1.25-mg, 2.5-mg, 5.0-mg, and 10-mg Ramipril tablet formulations to the corresponding strength Altace® capsules

E. LABELING

- a. The labeling is comparable to the labeling for the approved Altace® Capsules, with minor changes. The absence of a delay in absorption of ramipril as a result of coadministration of food described in the Altace® label has been removed. The relative lack of a food effect with the ramipril tablet versus the capsule is not likely to result in any significant difference in efficacy or safety profiles during chronic used. The food-effect was less evident for the metabolite ramiprilat.

Conclusion:

The firm has demonstrated the bioequivalence of a new dosage form of Ramipril 1.25-mg tablets to the approved 1.25-mg immediate release ramipril capsule, Altace®, manufactured by King Pharmaceuticals. The firm has also demonstrated the bioequivalence of a new dosage form of Ramipril 10-mg tablets to the approved 10-mg immediate release ramipril capsule, Altace®, manufactured by King Pharmaceuticals under fasted conditions. The effect of food on the bioavailability of the ramipril tablet has been determined and found to be different than the effect of food on the Altace® 10 mg capsule. The absence of a delay in absorption of ramipril as a result of co-administration of food described in the Altace® label has been removed. The relative lack of a food effect with the ramipril tablet versus the capsule is not likely to result in any significant difference in efficacy or safety profiles during chronic used. The food-effect was less evident for the metabolite ramiprilat. The labeling reflects this difference. A waiver for in vivo studies demonstrating the bioequivalence of the 2.5-mg and the 5.0 mg compared to the 10-mg ramipril tablet is acceptable. To support the absorption, distribution, metabolism and elimination portion of the label, the firm also submitted a literature search that was reviewed. The sponsor's proposed dissolution method of USP Apparatus 2 (Paddle) at 50 rpm, 500 mL of 0.1N HCl is

acceptable. The data indicate that the product can meet a specification of "Q"_____

Signatures

Reviewer: _____

Team Leader Concurrence _____

The CPB briefing was held on August 14, 2006, Attendees: Drs. N.Stockbridge, A. Karkowsky,
Jun Kitahara, Patrick Marroum, and Carol Noory

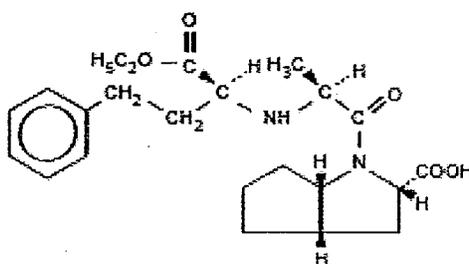
cc list: NDA 22-021; HFD-860: (Noory, Mehta); HFD-110

2. QBR

2.1. GENERAL ATTRIBUTES

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

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C. The chemical name of Ramipril is (2S,3aS,6aS)-1[(S)-N-[(S)-1-Carboxy-3-phenylpropyl] alanyl] octa hydrocyclopenta [b]pyrrole-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its molecular formula is $C_{23}H_{32}N_2O_5$, and its molecular weight is 416.5.

Ramipril is a pro-drug which is hydrolyzed after oral administration to form its active metabolite, ramiprilat. Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

The tablets are _____

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

Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Ramipril is indicated for the treatment of hypertension.

2.1.3. What is the solubility of ramipril?

Ramipril is freely soluble in methanol and sparingly soluble in water. The solubility of ramipril is summarized in the following table:

Table 1: Solubility of Ramipril

Buffer pH	pH of product in buffer	Solution Concentration
2.0	3.13	10 mg/mL Not soluble
4.01	4.15	10 mg/mL Not soluble
6.86	6.40	10 mg/mL Not soluble

Buffer pH	pH of product in buffer	Solution Concentration
9.18	7.96	10 mg/mL Not soluble
pH of % aqueous solution: 4.42		

2.1.4. What is the proposed route of administration?

Ramipril tablets are formulated to be taken orally with water.

2.2. CLINICAL PHARMACOLOGY

2.2.1. What are the pharmacokinetics of ramipril?

The sponsor referenced the clinical pharmacology of Altace® capsules and the pertinent literature.

Absorption:

Following oral administration of ramipril, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract. Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; in vitro, these percentages are independent of concentration over the range of 0.01 to 10 µg/mL.

Distribution:

Ramiprilat is distributed into a large peripheral compartment and subsequent binding to both plasma and tissue ACE. The half-life of this initial rapid decline phase is 2-4 hours. After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ramipril, especially at low doses (2.5 mg), but the difference is clinically insignificant.

Metabolism:

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive.

Elimination:

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9-18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug. After oral administration of ramipril, about 60% of the parent drug and its metabolites is eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Absolute Bioavailability: The absolute bioavailability of ramipril was 28% when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

2.2.2. What are the dose and dosing regimen and are there any unresolved dosing or administration issues?

The dose and dosing regimen are the same as labeled for Altace®. Blood pressure decreases associated with any dose of ramipril depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg once daily. For hypertension, the recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ramipril alone, a diuretic can be added.

After the initial dose of ramipril, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ramipril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

2.2.3 What are the pharmacodynamic responses of ramipril?

Single doses of ramipril of 2.5-20 mg produce approximately 60-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% approximately 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses is presumably a result of the saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

2.2.4. Are the pharmacokinetic parameters linear at steady-state?

The labeling of Altace® states that the blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range.

2.2.5. Was a waiver for a pediatric trial granted?

Yes, the sponsor's request for a waiver for pediatric studies was granted under section 2 of the Pediatric Research Equity Act. The sponsor received authorization from King Pharmaceuticals, Inc. to reference any pediatric studies submitted in the NDA 19-901 for Altace Capsules and to access the underlying raw data. The Division of Cardio-Renal Drug Products reviewed the waiver request and granted the waiver.

2.3. INTRINSIC FACTORS

Ramipril tablets are designed to be bioequivalent to Altace® capsules and the influence of any intrinsic factors would be expected to be the same as indicated for Altace® 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 Altace® capsules. These issues are covered in the labeling in the same way as for Altace® capsules.

2.5. GENERAL BIOPHARMACEUTICS

2.5.1. Was bioequivalence demonstrated for the new tablet dosage form when compared to the capsule dosage form, Altace®?

Yes, the sponsor proposes to market the ramipril tablets in strengths of 1.25-mg, 2.5-mg, 5.0-mg and 10-mg tablets to correspond to the Altace® marketed capsule strengths. The 1.25-mg ramipril tablets and the 10-mg tablets were compared to the corresponding strength Altace® capsules under fasting conditions. The sponsor conducted a two-way crossover, fasting bioequivalence study (Study 2835) to determine the bioequivalence of ramipril 10 mg tablets (highest strength) to the 10 mg Altace® capsules when administered under fasting conditions. The 10 mg ramipril tablets met the bioequivalence criteria when compared to Altace® 10 mg capsules. The 90% confidence intervals (CI) for the ramipril were (97.7-122.0%) for C_{max}; (94.8-109.4%) for AUC (0-t) and (89.1-106.3%) for AUC (0-inf). The ratio of means was 109% for C_{max}; 102% for AUC (0-t) and 89.1% for AUC (0-inf).

A two-way crossover, fasting bioequivalence study (Study 2970) was conducted to determine the bioequivalence of ramipril 1.25 mg tablets (lowest strength) compared to the 1.25 mg Altace® capsule when administered under fasting conditions. The results indicate that the 1.25 mg ramipril tablet met the bioequivalence confidence interval requirements when compared to Altace® 1.25 mg capsules. The 90% confidence intervals (CI) for the ramipril were (96.7-116.3%) for C_{max}; (95.9-110.3%) for AUC (0-t) and (95.4-110.3%) for AUC (0-inf). The ratio of means was 106% for C_{max}; 103% for AUC(0-t) and 103% for AUC(0-inf).

2.5.2. Are the 2.5 and 5.0 mg ramipril tablets bioequivalent to the 10 mg ramipril tablet?

Yes, a biowaiver was requested for the two middle strengths based on formulation proportionality compared to the 10 mg strengths ramipril tablet (Table 2) and dissolution similarity (Table 3). Dissolution profile of the 2.5-mg and 5.0 mg tablets were compared to the 10-mg ramipril tablet used in the bioavailability study. The dissolution method used was the proposed method, Paddle 50 rpm, 500 mL of 0.1N HCl.

Table 2: Composition of Ramipril Tablets

Component	1.25-mg tablet		2.5 mg tablet		5-mg tablet		10-mg tablet	
	Mg/tab	%	Mg/tab	%	Mg/tab	%	mg/tab	(%)
Ramipril (active ingredient) USP	—	—	—	—	—	—	—	—
Calcium sulfate dehydrate, USP	—	—	—	—	—	—	—	—
Starch, Pregelatinized USNF	—	—	—	—	—	—	—	—
Sodium Hydrogen Carbonate, USP	—	—	—	—	—	—	—	—

The key difference in performance between the two products was the effect of food on the absorption of the parent, ramipril. The food-effect was less evident for the metabolite ramiprilat. The post-prandial blunting of the peak concentration of the parent compound was associated with a significant delay in ramipril absorption from the Altace® reference capsules, as compared to the absorption under fasted conditions [Tmax fasted = 0.5 hours; Tmax fed = 2.4 hours]. This is noted in the labeling of the Altace® capsules. There is an absence of this delay in absorption of ramipril as a result co-administration of food with the ramipril tablets [Tmax fasted = 0.5 hours; Tmax fed = 1 hour]. The extent of absorption from the Altace® capsules was not affected to the same extent as the rate [AUC 0-t fasted = 16.4 ng-hr/mL; AUC 0-t fed = 16 ng-hr/mL]. The ramipril extent of absorption was greater from the tablets than from the Altace® capsules under fed conditions [AUC(0-t) for ramipril tablets was 19.2 ng-hr/mL and the AUC(0-t) for Altace was 16.2 ng-hr/mL]. The relative lack of a food effect with the ramipril tablet versus the capsule is not likely to result in any significant difference in efficacy or safety profiles during chronic used.

The labeling for Altace® states that “Following oral administration of Altace®, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.” The statement indicating that the _____ has been removed from the ramipril tablet labeling and the product can be dosed without regard to food.

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

The 1.25-mg and the 10-mg to-be-marketed formulations are identical to the formulations used in the pivotal clinical studies. The 2.5-mg and 5-mg to-be-marketed formulations are proportional to the 10-mg formulation and have similar dissolution profiles using the selected method. The sponsor tested several lots of each strength tablet, as well as each strength of Altace® capsules. The results are given in the following table.

Table 4: Profile comparison across commercial lots

LOT	STRENGTH	BATCH SIZE	10 MIN	15 MIN	20 MIN	25 MIN	30 MIN
1072168	1.25 mg						
D4001	1.25 mg						
F4001	1.25 mg						
F4002	1.25 mg						
1058906	2.5 mg						
D4002	2.5 mg						
F4003	2.5 mg						
F4004	2.5 mg						
1072168	5.0 mg						
D4003	5.0 mg						
F4005	5.0 mg						
F4006	5.0 mg						
RW1264	10.0 mg						
D4004	10.0 mg						
F4007	10.0 mg						
F4008	10.0 mg						

LOT	STRENGTH	BATCH SIZE	10 MIN	15 MIN	20 MIN	25 MIN	30 MIN

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

The sponsor's proposed dissolution method and tolerance uses the paddle method at 50 rpm with 500 mL 0.1N HCl and a tolerance specification of Q=_____ The dissolution method proposed was developed for the generic Cobalt ramipril capsules and is acceptable. However, the dissolution specification should be tightened. The dissolution data submitted indicates that the ramipril tablet can meet a more stringent requirement. Based on the data submitted, the agency recommended dissolution test and specification is Paddle, 50rpm, 500 mL 0.1 N HCl as the medium and "Q"_____

2.6. ANALYTICAL

2.6.1. Were the correct moieties identified and properly measured?

Yes, pharmacological testing has shown that Ramipril is a prodrug that is almost completely metabolized to its active diacid metabolite ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. Ramipril and ramiprilat were properly measures using a validated LC-MS/MS method.

2.6.2. What bioanalytical methods are used to assess concentrations?

The LC-MS/MS analytical method parameters are summarized in the following table (Table 5).

Table 5: Analytical Method Parameters

Parameter	N=	strength	Ramipril	Ramiprilat
Dates of analysis	9/25/04-9/17/04			
Matrix			Plasma	Plasma
Standards				
Standard correlation coefficient (SD)	N=3		0.995996	0.996816
Slope	N=3		0.627995	0.051590
LLQ			0.050 ng/mL	0.050 ng/mL
Linearity			0.050-51.259 ng/mL	0.050-51.179 ng/mL
Limit of Detection			0.12494 pg	1.00007 pg
Limit of Quantitation			0.050 ng/mL	0.050 ng/mL
Percent Recovery	10/7	0.05 ng/mL	100.0%	100.00
	10/9	0.100 ng/mL	101.0%	103.00
	8/8	0.200 ng/mL	98.5%	97.00
	8/7	0.400 ng/mL	105.25%	100.25
	9/10	1.602/1.599	101.8%	101.7%
	10/8	6.407/6.397 ng/mL	100.32%	100.15%
	10/9	25.630/25.589 ng/mL	102.4%	101.0%

Parameter	N=	strength	Ramipril	Ramiprilat
	10/8	51.259/51.179 ng/mL	91.9%	97.4%
Precision (%CV)	10/7	0.05 ng/mL	4.3%	8.6%
	10/9	0.100 ng/mL	10.9%	6.1%
	8/8	0.200 ng/mL	3.9%	5.3%
	8/7	0.400 ng/mL	6.8%	5.6%
	9/10	1.602/1.599	7.6%	7.5%
	10/8	6.407/6.397 ng/mL	5.8%	5.6%
	10/9	25.630/25.589 ng/mL	7.1%	9.7%
	10/8	51.259/51.179 ng/mL	4.0%	4.9%
Accuracy (%RE)	10/7	0.05 ng/mL	-0.7	-0.7
	10/9	0.100 ng/mL	0.8	3.3
	8/8	0.200 ng/mL	-1.7	-2.9
	8/7	0.400 ng/mL	5.3	0.3
	9/10	1.602/1.599	1.8	1.9
	10/8	6.407/6.397 ng/mL	0.3	0.3
	10/9	25.630/25.589 ng/mL	2.4	1.0
	10/8	51.259/51.179 ng/mL	-8.1	-2.6
Quality Control Samples				
Inter-batch Precision (%CV)	N=18		4.7 to 8.7%	1.4 to 12.8%
Inter-batch Accuracy (%RE)	N=18		-7.3 to 0.1%	-7.1 to 10.0%
Intra-batch Precision (%CV)	N=18		2.0 to 11.4%	3.1 to 13.4%
Intra-batch Accuracy (%RE)	N=18		-9.2 to 0.3%	-3.3 to 5.3%
Overall Precision (% CV)	N=18		6.6 to 11.4%	3.7 to 18.2%
Overall Accuracy (%RE)	N=30		-7.3 to 0.1%	-7.1 to 10.1%
Absolute Recovery	N=30		70.4% (8.6%)	66.9% (5.7%)
Stability				
Freeze/Thaw 3 cycles (% mean difference)	6	High/low	7.2%/-5.5%	11.0%/-3.6
Room Temperature (% mean difference)	6	High/low	-0.4%/-12.6%	4.6%/-10.7%

2.6.3. What information is available to assure that both the analytical assay and the clinical study were performed according to current GMPs and GCPs?

An Establishment Inspection was requested for the analytical site and the clinical site.

2.6.4. Did the Establishment Inspection report reveal any deficiencies that may affect the outcome of the bioequivalence study submitted by the firm?

The Establishment Inspection is pending.

6 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

4. APPENDIX

4.1 Sponsor's Proposed Label

4.2 Individual Studies

- 4.2.1 Clinical Study 2835 – 10 mg fasting bioequivalence study
- 4.2.2 Clinical Study 2836 – 10-mg non-fasting bioequivalence study
- 4.2.3 Clinical Study 2970 – 1.25-mg fasting bioequivalence study
- 4.2.4 Analytical Method Validation Report

4.3 Dissolution

4.4 Literature References

4.5 Filing Memo

Appendix 4.2.1 Clinical Study 2835

Bioequivalence study 10 mg fasting

TITLE: A two-way crossover, open-label, single-dose, fasting, bioequivalence study of ramipril 10 mg tablets versus Altace® 10 mg capsules in normal healthy non-smoking male and female subjects for the USA

INVESTIGATOR: _____

STUDY CENTER: _____

STUDY PERIOD: August 13, 2004 to October 1, 2004

OBJECTIVE: This study was designed to compare the rate and extent of absorption of ramipril 10 mg tablets versus Altace® 10 mg capsules under fasting conditions.

STUDY DESIGN: This is a two-way crossover, single dose, fasted bioequivalence study. Following an overnight fast of at least 10 hours, one 10 mg dose was administered orally with 240 mL of water.

TREATMENT:

Reference	Test
Altace 10 mg Capsules (King Pharmaceuticals, Inc) Lot RW1264	Ramipril 10 mg Tablets (Arrow Pharm (Malta) Ltd Lot D4004C

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected at 0.0 (predose), 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.67 (40 minutes), 0.83 (50 minutes), 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, and 144.0 hours post-dose.

SUBJECTS:

Thirty-four normal healthy, non-smoking male and female subjects (16 males and 18 females) were enrolled in the study. Twenty-nine subjects completed the study. It was calculated that 34 subjects would give a power of 80-90% to detect a difference in bioavailability.

ANALYTICAL METHOD:

A validated LC-MS/MS method was employed for the analysis of ramipril and its active metabolite ramiprilat in human plasma. Ramipril, ramiprilat and the internal standard were extracted by solid-phase extraction into an organic media from 0.5 mL of human plasma. An aliquot of this extract was injected into an HPLC system and detected using a tandem mass spectrometer. The analytes were separated by reverse-phase chromatography. Evaluation of the assay was carried out by the construction of an eight point calibration curve covering the range of

0.50 ng/mL to 51.259 ng/mL (in human plasma) for Ramipril and 0.050 ng/mL to 51.179 ng/mL (in human plasma) for Ramiprilat. A summary of the system performance is given in the following table.

Table 1: Analytical Method Performance

Parameter	N=	strength	Ramipril	Ramiprilat
Dates of analysis	10/20/2004 to 11/4/2004			
Analytical method			LC-MS/MS	LC-MS/MS
Matrix			Plasma	Plasma
Determination			Weighted linear regression analysis (1/conc 2)	
Standards				
Calibration curve range			0.50 ng/mL to 51.259 ng/mL	0.050 ng/mL to 51.179 ng/mL
Linearity n=17			0.995996	0.995535
Slope			0.522473	0.066114
%CV			24.9%	26.8
LLQ			0.50 ng/mL	0.50 ng/mL
Precision %CV	33/31	0.050/0.050	9.1	8.7
	32/25	0.10/0.100	6.7	8.2
	31/31	0.200/0.200	7.1	8.3
	33/30	0.400/0.400	6.5	7.1
	29/32	1.602/1.599	5.9	7.2
	32/33	6.407/6.397	7.2	8.7
	31/30	25.630/25.589	7.4	7.8
	32/33	51.259/51.179	6.7	6.4
Accuracy %RE	33/31	0.050/0.050	-1.3	-0.6
	32/25	0.10/0.100	1.7	0.5
	31/31	0.200/0.200	2.0	0.5
	33/30	0.400/0.400	0.6	0.9
	29/32	1.602/1.599	0.5	0.8
	32/33	6.407/6.397	0.6	-0.7
	31/30	25.630/25.589	-1.0	-1.1
	32/33	51.259/51.179	-2.9	-0.2
Quality Control Samples				
Percent recovery	34	0.15 ng/mL	98.7%	93.3%
		9.602 ng/mL	101.05%	93.9%
		38.407 ng/mL	100.2%	102.0%
Precision (%CV)	34	0.15 ng/mL	10.5%	14.3%
		9.602 ng/mL	9.5%	9.3%
		38.407 ng/mL	9.9%	8.4%
Accuracy (%RE)	34	0.15 ng/mL	-1.3%	-6.8%
		9.602 ng/mL	1.0%	-6.1%
		38.407 ng/mL	0.2%	-5.8%

Two calibration curves and duplicate QC samples (at three concentration levels) were analyzed along with each batch of the study sample. Peak area ratios were used to determine the concentrations of the standards, quality control samples, and the unknown study samples from the calibration curves.

PHARMACOKINETICS

Statistical Methods: Analysis of variance was performed using SAS GLM procedures. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% CI) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} between the test and reference formulations.

Results:

The summary of the pharmacokinetic parameters for ramipril and ramiprilat are given in the following table.

Table 2: Pharmacokinetic Results

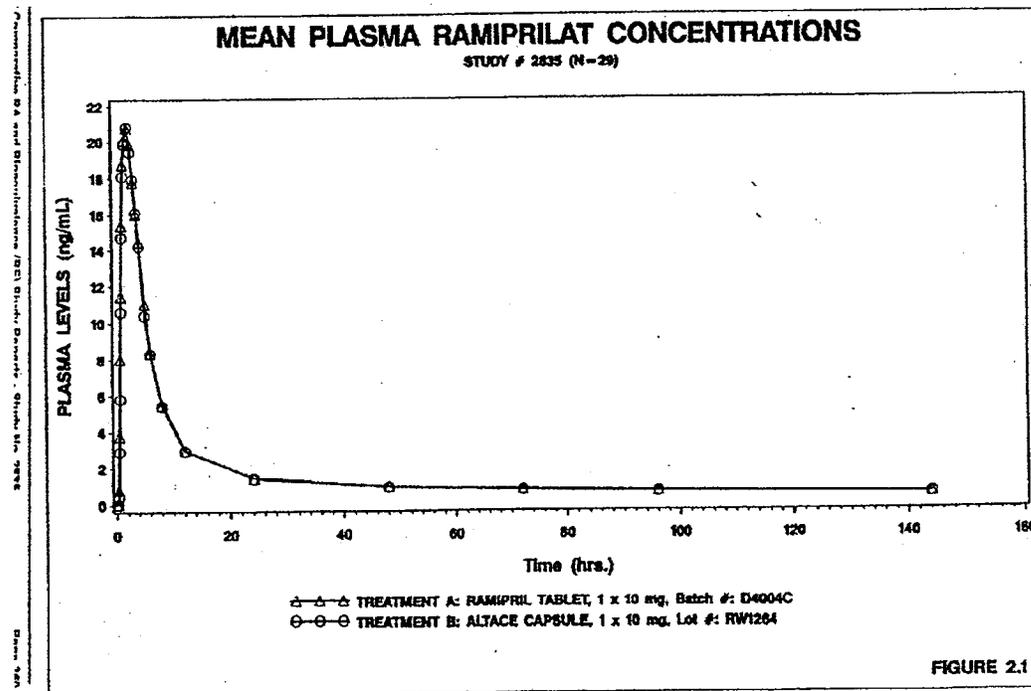
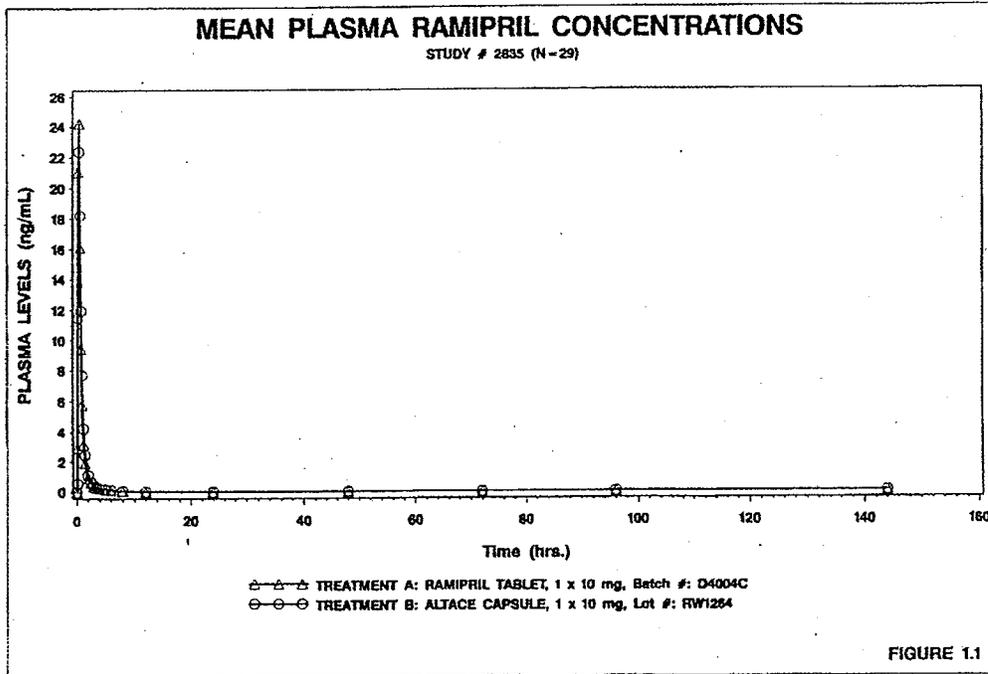
PHARMACOKINETIC RESULTS				
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	16.77 ± 5.51	16.40 ± 5.285	236.67 ± 54.34	229.42 ± 61.68
AUC (0-inf) ng-hr/mL	17.30 ± 5.44**	17.40 ± 4.85*		
Cmax (ng/mL)	27.58 ± 9.16	25.11 ± 8.47	23.72 ± 2.00	23.23 ± 13.32
Tmax	0.50 ± (0.33-0.67)	0.50 (0.33-1.00)*	3.53 (1.00-6.00)*	2.00 (1.00-6.03)*
T ½ (hr)	2.66 ± 1.58**	3.06 ± 4.46*	105.05 ± 37.90	109.85 ± 16.38*
Kel (hr-1)	3.70E-01 ± 2.45E-01	3.74E-01 ± 1.86E-01*	7.31E-03 ± 2.26E-03	6.45E-03 ± 9.61E-04
* n=29; ** n=28				

The statistical results are given in the following table. The mean data are shown graphically for ramipril and ramiprilat in the following figures.

Table 3: Bioequivalence Assessment

Parameter	90% CI		Ratio of Means		Intra-Subject Variation	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng-hr/mL	94.81% to 109.35%	98.04% to 109.78%	101.82%	103.74%	15.95%	12.64%
AUC (0-inf) ng-hr/mL	89.12% to 106.25%		97.31%		14.60%	
Cmax (ng/mL)	97.73% to 122.04%	91.56% to 116.03%	109.21%	103.07%	24.82%	26.45%

The in vivo profiles for ramipril and ramiprilat are shown in the following figures.



SAFETY ASSESSMENT

There were no serious adverse events reported and two subjects withdrew due to AEs. There were a total of eighteen AEs reported by 9 subjects during the study. The relationship to the study drug was considered "possibly" responsible for one of the AEs. One subject was lost to

follow-up; one subject had an AE that is ongoing, all other subjects recovered completely from their AEs. No significant safety concerns were raised.

CONCLUSION

Ramipril-Study 2835

Based on the statistical results for ramipril, the 90% confidence intervals for AUC_{0-t}, AUC_{0-inf} and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} were [94.81-109.35%], [89.12-106.25%], and [97.97-122.04%], respectively. The ratio of geometric means were 1.0, 1.0, and 1.1 for AUC_{0-t}, AUC_{0-inf} and C_{max} respectively. There was no significant difference in the *k_{el}* and *t*_{1/2} values between treatments (*p*>0.05) for ramipril. The total exposure to ramipril was similar between the two treatments. The intra-subject variation for ramipril ranged from 14.6% to 24.82%.

Ramiprilat-Study 2835

The 90% confidence intervals for AUC_{0-t} and C_{max} of the active metabolite, ramiprilat, were within 80% - 125%. Based on the statistical results for ramiprilat, the 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test compared to the reference formulation were [98.04-109.78] and [91.56-116.03%], respectively. There was no significant difference in the *k_{el}* and *t*_{1/2} values between treatments (*p*>0.05) for ramiprilat. The intra-subject variations for all parameters for ramiprilat were between 12.64% and 26.45%. Due to the long elimination half-life of ramiprilat, the percentage of extrapolation for AUC_{0-inf} was greater than 20% for many subjects, and the average ratio of AUC_{0-t} to AUC_{0-inf} was approximately 74%. Therefore, the results of AUC_{0-inf} were not used for assessment of bioequivalence.

Safety:

There were no serious adverse events reported. No significant safety concerns were raised.

Appendix 4.1.2
Clinical Study 2836
Bioequivalence Study 10 mg Fed

TITLE: A two-way crossover, open-label, single-dose, fed, bioequivalence study of ramipril 10 mg tablets versus Altace® 10-mg capsules in normal healthy non-smoking male and female subjects for the USA

INVESTIGATOR: _____

STUDY CENTER: _____

STUDY PERIOD: October 15, 2004 to December 3, 2004

OBJECTIVE: This study was designed to compare the rate and extent of absorption of ramipril 10 mg tablets versus Altace® 10 mg capsules under fed conditions.

STUDY DESIGN: The study is a two-way crossover, single dose, fed bioequivalence study. Following an overnight fast of at least 10 hours, one 10 mg dose was administered orally with 240 mL of water 30 minutes after the start of a high-fat breakfast. The high fat breakfast consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of milk. This is the high-fat meal described in the FDA Guidance Food-Effect Bioavailability and Fed Bioequivalence Studies.

TREATMENT: Ramipril 10 mg Tablets (Arrow Pharm (Malta) Ltd. Lot D4004C
Altace® 10 mg Capsules (King Pharmaceuticals, Inc) Lot RW1264

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected at 0.0 (predose), 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.67 (40 minutes), 0.83 (50 minutes), 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, and 144.0 hours post-dose.

SUBJECTS: Thirty-two normal healthy, non-smoking male and female subjects (14 males and 18 females) were enrolled in the study. Thirty subjects completed the study. It was calculated that 34 subjects would give a power of 80-90% to be able to detect a food effect.

ANALYTICAL METHOD: A validated LC-MS/MS method was employed for the analysis of ramipril and its active metabolite ramiprilat in human plasma. Ramipril, ramiprilat and the internal standard were extracted by solid-phase extraction into an organic media from 0.5 mL of human plasma. An aliquot of this extract was injected into a high performance liquid chromatography system and detected using a tandem mass spectrometer. The analytes were separated by reverse-phase chromatography. Evaluation of the assay was carried out by the construction of an eight point calibration curve covering the range of 0.50 ng/mL to 51.259 ng/mL (in human plasma) for

Ramipril and _____ (in human plasma) for Ramiprilat: A summary of the system performance is given in the following table.

Table 1: Analytical Method Performance

Parameter	N=	strength	Ramipril	Ramiprilat
Dates of analysis	12/6/2004 to 1/5/2005			
Analytical method			LC-MS/MS	LC-MS/MS
Matrix			Plasma	Plasma
Determination			Weighted linear regression analysis (1/conc 2)	
Standards				
Calibration curve range			0.50 ng/mL to 51.259 ng/mL	0.050 ng/mL to 51.179 ng/mL
Linearity n=32			0.995350	0.995535
Slope			0.454225	0.066114
%CV			33.2%	26.8
Precision %CV	61/59	0.050/0.050	7.4	8.6
	59/57	0.10/0.100	6.3	7.6
	59/59	0.200/0.200	6.7	6.4
	60/60	0.400/0.400	6.5	6.4
	59/62	1.602/1.599	6.6	6.8
	61/57	6.407/6.397	6.4	6.0
	60/60	25.630/25.589	6.9	6.8
	61/61	51.259/51.179	7.4	7.5
Accuracy %RE	61/59	0.050/0.050	-1.5	-0.2
	59/57	0.10/0.100	2.1	-0.7
	59/59	0.200/0.200	1.2	1.3
	60/60	0.400/0.400	1.7	1.4
	59/62	1.602/1.599	0.8	0.4
	61/57	6.407/6.397	-0.5	-1.9
	60/60	25.630/25.589	-1.2	-0.4
	61/61	51.259/51.179	-2.4	-0.1
Quality Control Samples				
Percent recovery (%)	64	0.15 ng/mL	99.3	95.3
		9.602 ng/mL	99.5	96.8
		38.407 ng/mL	99.3	97.2
Precision (%CV)	64	0.15 ng/mL	8.4	8.7
		9.602 ng/mL	6.5	6.7
		38.407 ng/mL	7.1	7.6
Accuracy (%RE)	64	0.15 ng/mL	-0.7	-5.0
		9.602 ng/mL	-0.5	-3.1
		38.407 ng/mL	-0.7	-2.8

Two calibration curves and duplicate QC samples (at three concentration levels) were analyzed along with each batch of the study sample. Peak area ratios were used to determine the concentrations of the standards, quality control samples, and the unknown study samples from the calibration curves.

PHARMACOKINETICS

Statistical Methods: Analysis of variance was performed using SAS GLM procedures. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% CI) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} between the test and reference formulations.

Results:

The summary of the PK parameters for ramipril and ramiprilat are given in the following table.

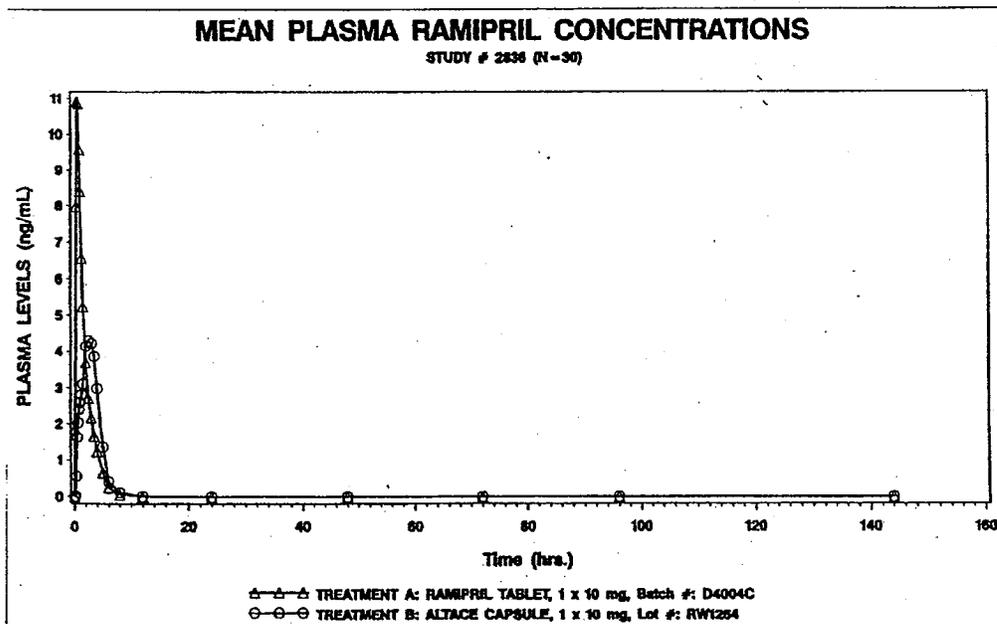
Table 2: Pharmacokinetic Results

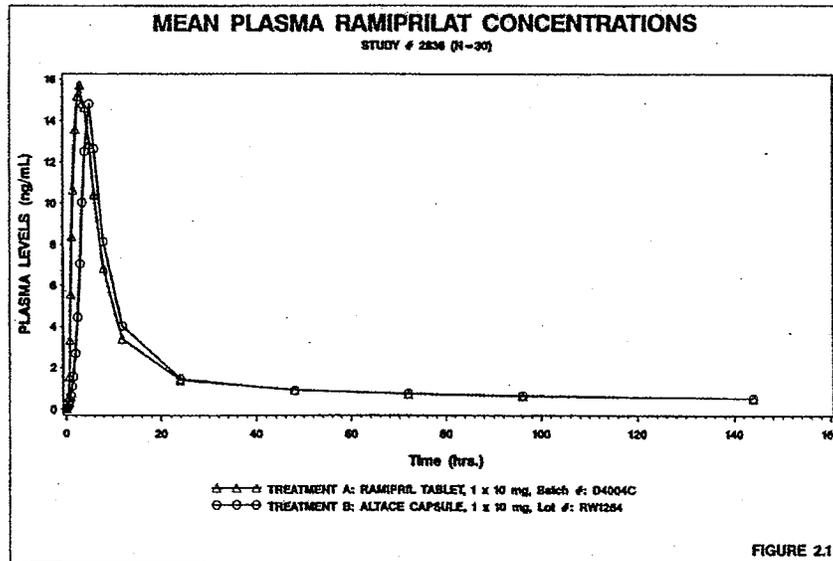
Pharmacokinetic parameter	Ramipril	Altace ramipril	Ramiprilat	Altace ramiprilat
AUC (0-t) ng-hr/mL	19.23 ± 7.27	16.15 ± 5.79	226.86 ± 59.70	216.67 ± 50.39
AUC (0-inf) ng-hr/mL	19.36 ± 7.29	16.64 ± 5.64*	328.85 ± 90.98**	312.55 ± 73.20*
Cmax (ng/mL)	15.13 ± 8.46	6.58 ± 2.81	19.17 ± 10.08	15.71 ± 6.35
Tmax	0.99 ± 0.74 (0.67)	2.39 ± 0.93 (2.25)	3.53 ± 1.47 (3.50)	4.93 ± 0.98 (5.00)
T ½ (hr)	0.97 ± 0.26	0.90 ± 0.27*	120.19 ± 36.06**	122.06 ± 38.13*
Kel (hr-1)	7.61E-01 ± 1.88E-01	8.38E-01 ± 2.64E-01*	6.20E-03 ± 1.62E-03**	6.17E-03 ± 1.82E-03
* n=29; ** n=28				

A summary of the statistical results and figures showing the mean ramipril and ramiprilat data are given in the following table and figures.

Table 3: Bioequivalence Assessment

Parameter	90% CI		Ratio of Means		Intra-Subject Variation	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng-hr/mL	112.37% to 125.69%	100.59% to 107.52%	118.84%	104.00%	12.76%	7.59%
AUC (0-inf) ng-hr/mL	110.92% to 123.22%	94.67% to 107.13%	116.91%	100.71%	11.75%	13.28%
Cmax (ng/mL)	171.04% to 262.72%	106.27% to 128.39%	211.98%	116.81%	48.86%	21.53%





SAFETY ASSESSMENT

There were no serious adverse events reported and no subjects withdrew due to AEs. There were a total of ten AEs reported by 8 subjects during the study. The relationship to the study drug was considered “probably” or “possibly” responsible for two of the AEs. All subjects recovered completely from their AEs except for two subjects that were unknown due to lost to follow-up. No significant safety concerns were raised.

CONCLUSION

Ramipril-Study 2836

1. Based on the statistical results for ramipril, the 90% confidence interval for AUC_{0-inf} was 110.92-123.22%, within 80% to 125%. The 90% CI for the AUC_{0-t} and C_{max} of the test compared to the reference formulation was found not to be within the range of 80% -125%. The 90% confidence intervals for AUC_{0-t} and C_{max} were [112.37-125.69] and [171.04-262.72%], respectively.
2. The ratio for AUC_{0-inf} was 1.2. The ratio of means for the AUC_{0-t} and C_{max} were 1.2 and 2.1 respectively.
3. The intra-subject variation was high for C_{max} [48.86%]. T_{max} was 0.99 hours for ramipril and 2.39 hours for Altace® capsules.
4. There was no significant difference in the k_{el} and t_{1/2} values between treatments (p>0.05) for ramipril.

Ramiprilat-Study 2836

1. Based on the statistical results for ramipril, the 90% confidence intervals for AUC_{0-t} and AUC_{0-inf} were within 80% to 125%. The 90% confidence intervals were [100.59-107.52%] and [94.67-107.13%], for AUC_{0-t} and AUC_{0-inf}, respectively. The ratio of the relative means for AUC_{0-t} and AUC_{0-inf} were 1.0 and 1.0 respectively.

2. The 90% confidence interval for C_{max} was not within 80-125%. The 90% confidence interval for C_{max} was [106.27-128.39%], slightly above the upper level to determine bioequivalence. The ratio of means for C_{max} was 1.2.
3. The intra-subject variation for C_{max} was 21.53%.
4. There was not significant difference between t_{1/2} and K_{el}.

The absence of food effect on BA is not established if the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80-125 percent for either AUC_{0-inf} (AUC_{0-t} when appropriate) or C_{max}. In this case, the evaluation of a food effect was based on comparison of the test product (ramipril tablets) given under fed conditions compared to the reference product (Altace®) given under fed conditions. The effect of food on the bioavailability of the 10-mg ramipril tablet is different than the effect of food on the Altace® 10 mg capsule.

The bioequivalence assessment determined that the 10 mg ramipril tablet C_{max} did not meet the bioequivalence confidence interval requirements when compared to Altace® 10 mg capsules. The mean AUC (0-inf) value was within the 80-125% bioequivalence; At 126%, the AUC (0-t) confidence interval was slightly higher than the acceptable limit of 125%. The 90% confidence intervals (CI) for C_{max} of ramipril was (171.0-262.7%). This is well above the acceptable limit of 125%. This effect is not seen with the active metabolite, ramiprilat. The bioequivalence assessment for ramiprilat determined that the active metabolite ramiprilat did meet the bioequivalence requirements.

The key difference in performance between the two products was the effect of food on the absorption of the parent, ramipril. A possible explanation for this is the post-prandial blunting of the peak concentration of the parent compound associated with a significant delay in ramipril absorption from the Altace® reference capsules, as compared to the absorption under fasted conditions [T_{max} fasted = 0.5 hours; T_{max} fed = 2.4 hours]. This is noted in the labeling of the Altace® capsules. There is an absence of this delay in absorption of ramipril as a result co-administration of food with the ramipril tablets [T_{max} fasted = 0.5 hours; T_{max} fed = 1 hour]. The extent of absorption from the Altace® capsules was not affected to the same extent as the rate [AUC 0-t fasted = 16.4; AUC 0-t fed = 16]. The ramipril extent of absorption was greater from the tablets than from the Altace® capsules. The relative lack of a food effect with the ramipril tablet versus the capsule is not likely to result in any significant difference in efficacy or safety profiles during chronic use.

The labeling for Altace® states that "Following oral administration of Altace®, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced." The statement indicating that the _____ has been removed from the ramipril tablet labeling and the product can be dosed without regard to food.

Safety:

There were no serious adverse events reported. No significant safety concerns were raised.

Appendix 4.2.3 Clinical Study 2970
Bioequivalence Study 1.25 mg Fasting

TITLE: A two-way crossover, open-label, single-dose, fasting, bioequivalence study of ramipril 1.25 mg tablets versus Altace® 1.25 mg capsules in normal healthy non-smoking male and female subjects for the USA

INVESTIGATOR: _____

STUDY CENTER: _____

STUDY PERIOD: October 30, 2004 to December 24, 2004

OBJECTIVE: This study was designed to compare the rate and extent of absorption of ramipril 1.25 mg tablets versus Altace 1.25 mg capsules under fasting conditions.

STUDY DESIGN: The study is a two-way crossover, single dose fasting bioequivalence study. Following an overnight fast of at least 10 hours, one 1.25 mg dose was administered orally with 240 mL of water.

TREATMENT: Ramipril 1.25 mg Tablets (Arrow Pharm (Malta) Ltd. Lot D4001C
Altace® 1.25 mg Capsules (King Pharmaceuticals, Inc) Lot 1072168

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected at 0.0 (predose), 0.17 (10 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.67 (40 minutes), 0.83 (50 minutes), 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0, 96.0, and 144.0 hours post-dose.

SUBJECTS: Thirty-four normal healthy, non-smoking male and female subjects (16 males and 18 females) were enrolled in the study. Twenty-nine subjects completed the study. Data was calculated on 30 subjects (one subject had a sufficient number of data points to allow inclusion into the analysis. It was calculated that 34 subjects would give a power of 80-90% to be able to detect a difference between treatments.

ANALYTICAL METHOD: A validated LC-MS/MS method was used for the analysis of ramipril and its active metabolite ramiprilat in human plasma. Ramipril, ramiprilat and the internal standard were extracted by solid phase-extraction into an organic media from 0.5 mL of human plasma. An aliquot of this extract was injected into a HPLC system and detected using a tandem mass spectrometer. The analytes were separated by reverse-phase chromatography. Evaluation of the assay was carried out by the construction of an eight-point calibration curve covering the range of 0.50 ng/mL to 51.259 ng/mL (in human plasma) for Ramipril and 0.050 ng/mL to 51.179 ng/mL (in human plasma) for Ramiprilat. A summary of the system performance is given in the following table.

The summary of the pharmacokinetic parameters for ramipril and ramiprilat are given in the following table.

Table 2: Pharmacokinetic Results for 1.25 mg Ramipril Dose

PHARMACOKINETIC PARAMETER	RAMIPRIL	ALTACE RAMIPRIL	RAMIPRILAT	ALTACE RAMIPRILAT
AUC (0-t) ng-hr/mL	1.81 ± 0.93	1.75 ± 0.81	70.36 ± 20.73	74.81 ± 20.03
AUC (0-inf) ng-hr/mL	1.88 ± 0.96*	1.82 ± 0.86*	177.11 ± 97.10*	166.01 ± 52.83*
Cmax (ng/mL)	2.60 ± 1.20	2.50 ± 1.25	1.14 ± 0.48	1.16 ± 0.37
Tmax	0.50 (0.33-0.82)	0.53 (0.33-1.50)	3.50 (1.50-12.00)	3.25 (1.50-6.00)
T ½ (hr)	0.65 ± 0.82*	0.75 ± 1.18*	201.35 ± 113.22*	179.27 ± 78.72*
Kel (hr-1)	1.65E-01 ± 6.75E-01	1.55E-01 ± 5.74E-01*	4.41E-03 ± 2.12E-03**	4.41E-03 ± 1.40E-03**
* n=29; ** n=28				

The summary of the statistical analysis is given in Table 3. The concentration-time curves for ramipril and ramiprilat are shown in the following figures.

Table 3: Bioequivalence Assessment

PARAMETER	90% CI		RATIO OF MEANS		INTRA-SUBJECT VARIATION	
	Ramipril	Ramiprilat	Ramipril	Ramiprilat	Ramipril	Ramiprilat
AUC (0-t) ng-hr/mL	95.95% to 110.15%	87.61% to 99.34%	102.80%	93.29%	15.71%	14.29%
AUC (0-inf) ng-hr/mL	95.44% to 110.24%	89.50% to 120.20%	102.57%	103.72%	16.11%	27.61%
Cmax (ng/mL)	96.65% to 116.30%	90.87% to 102.93%	106.02%	96.71%	21.08%	14.19%

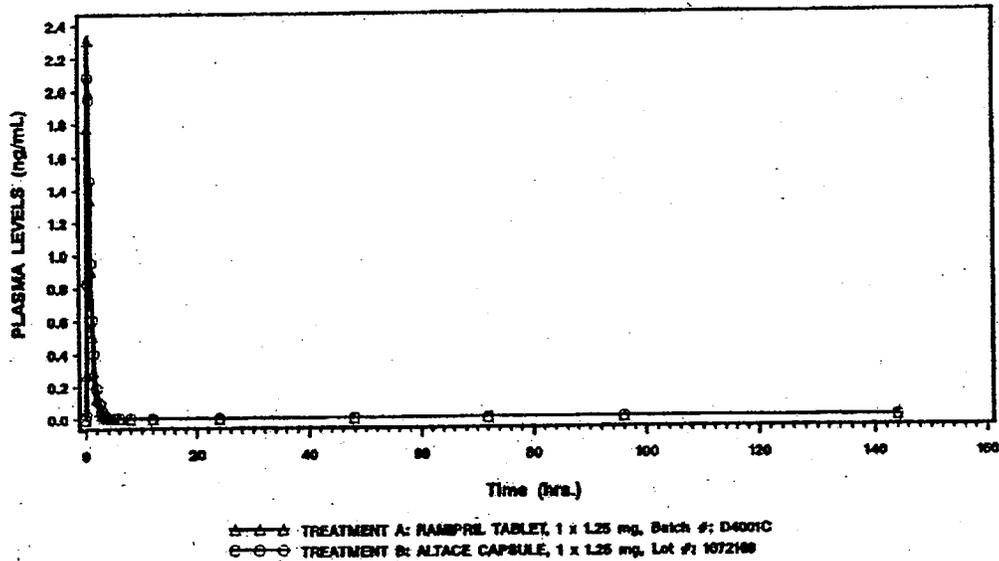


Figure 1: Mean Plasma Ramipril Concentrations (n=30)

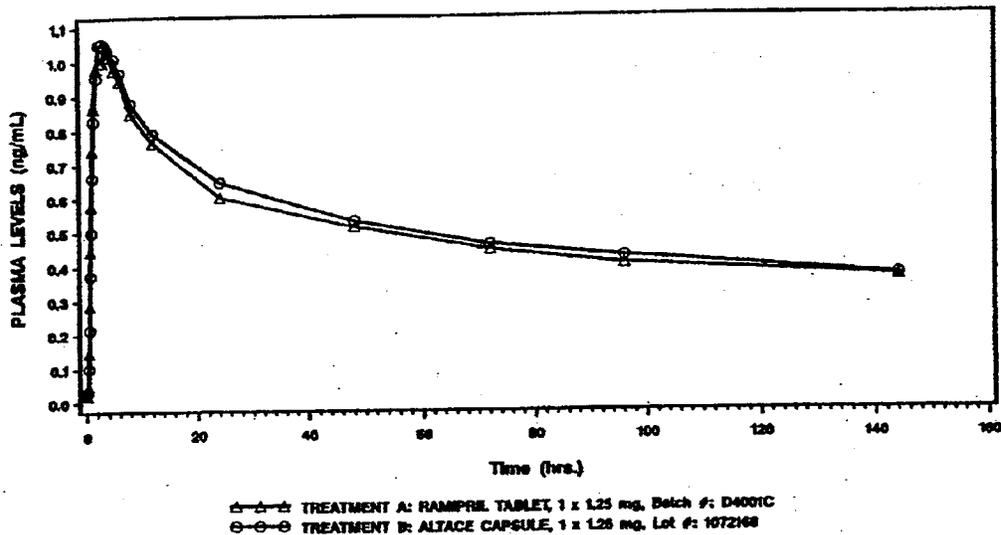


Figure 2: Mean plasma Ramiprilat Concentrations (n=30)

SAFETY ASSESSMENT

There were no serious adverse events reported and no subjects withdrew due to AEs. There were a total of twenty-four AEs reported by 11 subjects during the study. The drug was considered “possibly” responsible for five of the AEs. All subjects recovered completely from their AEs except for three subjects that were not available for follow-up. No significant safety concerns were raised. Eight subjects experience a total of 14 AEs following administration of Ramipril tablets (Treatment A). There were two instances of ketone bodies urine positive and two instances of dizziness. There was one instance each of menstrual cramps, headache, vomiting (two episodes), serum potassium decreased, urinary protein increased, loose stool (one episode), platelets decreased, alanine aminotransferase (ALT) increased, blood alkaline phosphatase increased, and urobilinogen urine positive.

CONCLUSION

Ramipril-Study 2970

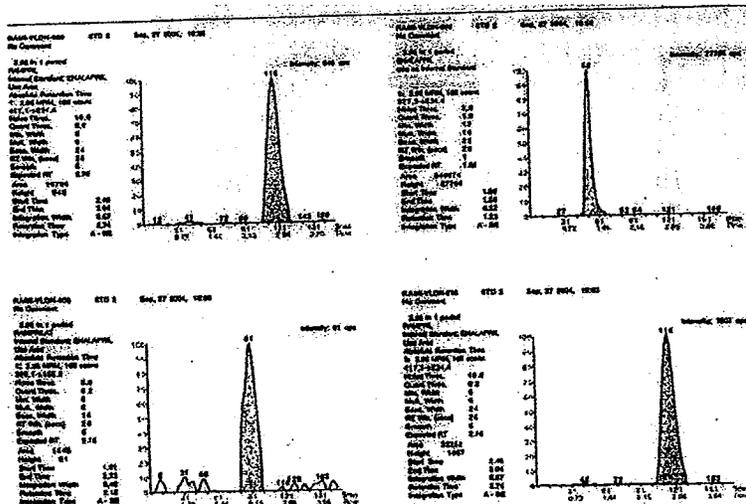
Based on the statistical results of ramipril, the 90% confidence intervals for AUC0-t, AUC0-inf, and Cmax of the test compared to the reference formulation was found to be within the range of 80% -125%. The 90% confidence intervals for AUC0-t, AUC0-inf, and Cmax were (95.95-110.15%), [95.44-110.24%], and [96.65-116.30%], respectively. The statistical results indicate that the geometric means ratio for AUC0-t, AUC0-inf, and Cmax were 1.0, 1.0, and 1.1, respectively. There was no significant difference in the kel and t ½ values between treatments (p>0.05) for ramipril. The intra-subject variation for Cmax of ramipril is significantly elevated.

Ramiprilat-Study 2970

Based on the statistical results of ramiprilat, the 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} of the test compared to the reference formulation was found to be within the range of 80% -125%. The 90% confidence intervals of the geometric means ratio for AUC_{0-t}, AUC_{0-inf}, and C_{max} were (87.61-99.34%), [89.50-120.20%], and [90.87-102.93%], respectively. The ratio of geometric means for AUC_{0-t}, AUC_{0-inf}, and C_{max} were 0.9, 1.0, and 1.1, respectively. There was no significant difference in the k_{el} and t_{1/2} values between treatments (p>0.05) for ramiprilat.

Safety-Study 2970:

No serious AEs were reported and no subjects discontinued the study due to AEs. No significant safety concerns were raised.



The samples were assessed for stability under several conditions:

Freeze/Thaw Stability

Freeze-Thaw Stability at $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$ for Ramipril and Ramiprilat in human plasma was determined with the quality control samples at 2 levels, QC low and QC High. After undergoing 1, 2 and 3 Freeze/Thaw cycles, these samples were analyzed and compared with freshly prepared QC LW and QC HIGH samples.

In-Process Stability

In-process stability was demonstrated by a set of QC samples at QC LOW and QC HIGH that were left on bench top for approximately 4 hours prior to extraction. These were analyzed against a set that were extracted immediately after thawing. Ramipril and Ramiprilat showed no loss of response within four hours at room temperature.

Autosampler Stability:

For each of the QC levels, six quality control samples were extracted and reconstituted. The six samples were pooled into one tube and divided into 3 autosampler vials stored at room temperature. A volume for injection from each vial was injected at 0 hours. A second volume was injected after approximately 22 hours; a third after 42 hours and a fourth after 68 hours. The time elapsed for injections are approximate calculations based on the shortest period of time between the first injection of the autosampler stability at 0 hours and at each of the run times. These results were compared with the mean of the zero hour samples. Ramipril and Ramiprilat are stable in extracted samples for up to 68 hours at room temperature.

Long-term Stability:

Long term stability of Ramipril and Ramiprilat in human plasma at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ was determined with quality control samples at QC LOW and QC HIGH levels. Aged QC LOW and QC HIGH samples were analyzed along with freshly prepared QC Low and QC HIGH samples. Ramipril and Ramiprilat are stable in plasma at $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$ for up to 238 days.

Conclusion:

The method was determined to be robust and selective for ramipril and ramiprilat.

4.3 DISSOLUTION

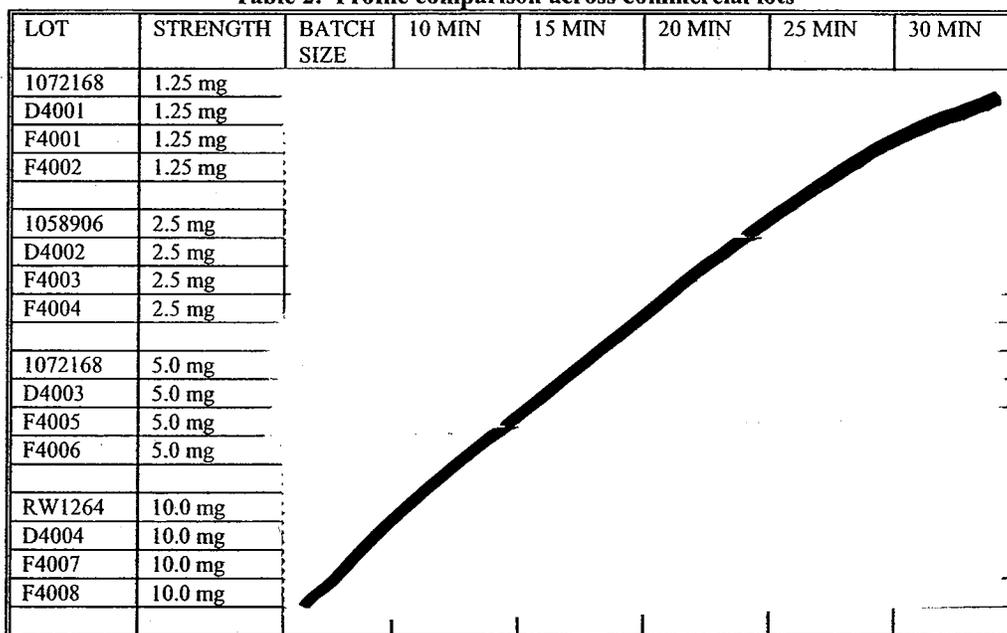
The sponsor conducted a solubility study using the ramipril drug substance. The results of the study are shown in the following table (Table 1).

Table 6: Solubility of Ramipril

Buffer pH	pH of product in buffer	Solution Concentration
2.0	3.13	10 mg/mL Not soluble
4.01	4.15	10 mg/mL Not soluble
6.86	6.40	10 mg/mL Not soluble
9.18	7.96	10 mg/mL Not soluble
pH of % aqueous solution: 4.42		

Ramipril is freely soluble in methanol and sparingly soluble in water. The approved dissolution method for Altace® immediate release capsules uses the paddle method, 50 rpm and 0.1N HCL as the media. Cobalt developed a dissolution method for their approved ANDA ramipril capsules using the paddle method with 0.1M HCl as the media. This method was selected for ramipril tablets as well. The sponsor tested three lots of each strength tablet, as well as one lot of each strength of Altace® capsules. The results are given in the following table.

Table 2: Profile comparison across commercial lots



The sponsor has proposed a dissolution specification of Q=_____ The results indicate that the ramipril tablets can meet a specification of Q=_____. The following dissolution method and specification are recommended for ramipril tablets:

Apparatus: Paddle Method
 Rpm: 50 rpm
 Media: 0.1N HCl
 Volume: 500 mL
 Specification: Q=_____

4.4 LITERATURE REFERENCES

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 - Ramipril produced a steady decrease in blood pressure without changing heart rate.
 46. Todd PA, Benfield P. *Ramipril. A review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders*. Drugs. 1990 Jan;39(1):110-35. Review. ADIS Drug Information Services, Auckland, New Zealand.
 - Hypertensive patients given daily doses in the range 2.5 to 20 mg are usually effective in reducing high blood pressure and maintaining satisfactory control during long term treatment. Patients who do not respond adequately to monotherapy with ramipril usually respond with the addition of a diuretic such as hydrochlorothiazide or piretanide. Ramipril 5 to 10 mg once daily shows comparable antihypertensive efficacy to usual therapeutic dosages of captopril, enalapril and atenolol in patients with mild to moderate essential hypertension. Ramipril will likely represent a useful alternative ACE inhibitor for use in patients with hypertension or congestive heart failure.
 47. Tu K, Mamdani M, Kopp A, Lee D. *Comparison of angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure*. Am J Cardiol. 2005 Jan 15;95(2):283-6. Institute for Clinical Evaluative Sciences, G106-2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.
 - Relative to those initiated on enalapril, no significant differences in the combined end point of readmission to the hospital for CHF or mortality were observed among users of lisinopril, ramipril, or other ACE inhibitors. In terms of effectiveness for the treatment of patients with CHF, the findings of this study suggest a class effect among ACE inhibitors
 48. van Griensven JM, Schoemaker RC, Cohen AF, Luus HG, Seibert-Grafe M, Rothig HJ. *Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril*. Eur J Clin Pharmacol. 1995;47(6):513-8. Centre for Human Drug Research, University Hospital Leiden, The Netherlands.
 - The pharmacokinetics and pharmacodynamics of the prodrug ramipril and its active metabolite ramiprilat were investigated. Ramiprilat renal clearance was concentration dependent. The biological availability of ramipril can best be judged by ramiprilat AUC, urinary recovery of ramipril and metabolites, or ACE inhibition over 24 h. It is concluded that the bioavailability of oral ramipril seems to be in the range of 44-66%.
 49. Vasmant D, Lendresse P, Lemarie JC, Gallet M. *Comparison of response rates to the angiotensin-converting enzyme inhibitor ramipril in mild-to-moderate hypertension in a double-blind, parallel-group study and an open single-blind study*. J Cardiovasc Pharmacol. 1991;18 Suppl 2:S144-6. Laboratoires Hoechst, Paris La Defense, France.
 - ramipril was studied to identify the minimum effective dose for the management of mild-to-moderate hypertension. It is concluded that study methodology apparently influences efficacy and tolerability.
 50. Willenheimer R, Rydberg E, Oberg L, Juul-Moller S, Erhardt L. *ACE inhibition with ramipril improves left ventricular function at rest and post exercise in patients with stable ischaemic heart disease and preserved left ventricular systolic function*. Eur Heart J. 1999 Nov;20(22):1647-56. Department of Cardiology, Malmo University Hospital, Lund University, Malmo, Sweden.

- Six months ramipril treatment in patients with stable ischaemic heart disease and preserved left ventricular systolic function improved resting left ventricular function and reduced the exercise induced diastolic filling abnormalities usually seen in these patients.
51. Wu N, Zhu JR, Chen KA. *Tolerability of ramipril 10 mg/day in high-risk Chinese patients*. Clin Drug Invest 2002;22(11):771-81
52. Wuhl E, Mehls O, Schaefer F; ESCAPE Trial Group. *Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure*. Kidney Int. 2004 Aug;66(2):768-76. Division of Pediatric Nephrology, University Children's Hospital, University of Heidelberg, Heidelberg, Germany.
- Ramipril appears to be an effective and safe antihypertensive and antiproteinuric agent in children with CRF-associated hypertension. The BP lowering and antiproteinuric effects are greatest in severely hypertensive and proteinuric children.
53. Yeung E, Wong FS, Wanless IR, Shiota K, Guindi M, Joshi S, Gardiner G. *Ramipril-associated hepatotoxicity*. Arch Pathol Lab Med. 2003 Nov;127(11):1493-7. Departments of Medicine, Toronto General Hospital, Toronto, Ontario, Canada.
- Prolonged cholestatic hepatitis and biliary cirrhosis may result from the use of ramipril. Monitoring of liver enzymes is advisable for patients starting on ramipril.
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4.5 FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
<i>General Information About the Submission</i>				
	Information		Information	
NDA Number	22-021	Brand Name	TBD	
OCPB Division (I, II, III)	I	Generic Name	Ramipril	
Medical Division	Cardio-Renal	Drug Class		
OCPB Reviewer	Carol Noory	Indication(s)	Hypertension	
OCPB Team Leader	Patrick Marroum	Dosage Form	1.25, 2.5, 5, and 10 mg T	
		Dosing Regimen		
Date of Submission	01/09/2006	Route of Administration	Oral	
Estimated Due Date of OCPB Review	08/01/2006	Sponsor	Cobalt Pharmaceuticals, Inc	
PDUFA Due Date	11/30/2006	Priority Classification	S	
Division Due Date	August 2006			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"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				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
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:	2			
replicate design; single / multi dose:				
Food-drug interaction studies:	1			
Dissolution:	1			
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	53			
Total Number of Studies				
Filability and QBR comments				
		"X" if yes	Comments	
Application filable ?			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)	<ol style="list-style-type: none"> 1. BE of parent and metabolite to RLD of 1.25 mg and 10 mg 2. Linearity of dose response 3. Proportionality of Formulations 4. Acceptance of Biowaiver request 5. Similar dissolution profiles. 6. Food effect of parent and metabolite 7. Acceptable label 			
Other comments or information not included above	ANDA for Cobalt ramipril- hard gelatin capsules ANDA 076549			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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

/s/

Carol Noory
8/14/2006 06:17:59 PM
BIOPHARMACEUTICS

Patrick Marroum
8/15/2006 02:18:37 PM
BIOPHARMACEUTICS