CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-909

Bioequivalence Review(s)

J. Barlow

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-909 APPLICANT: CHEMINOR DRUGS LTD.

DRUG PRODUCT: ENALAPRIL MALEATE /HYDROCHLOROTHIAZIDE TABLETS
5 mg/12.5 mg & 10 mg/25 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing should be incorporated into your stability and quality control programs as specified in USP XXIV.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara Myers Davit

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Enalapril Maleate Hydrochlorothiazide
Tablets 5 mg/12.5 mg & 10 mg/25 mg
ANDA #: 75909
Reviewer: Patrick Nwakama
File Name: 75909SDW.600

Reddy-Cheminor, Ltd
66 South Maple Avenue
Ridgewood, NJ 07450
Submission Date:
June 16, 2000
September 20, 2000(Amendment)

REVIEW OF TWO *IN VIVO* BIOEQUIVALENCE STUDIES, DISSOLUTION DATA AND WAIVER REQUEST

The firm has submitted two in vivo bioequivalence (single-dose fasting and single-dose non-fasting) studies comparing its test product, Enalapril Maleate Hydrochlorothiazide Tablet, 10 mg/25 mg, to the reference listed drug, Merck's Vaseretic^{R} Tablets, 10 mg/25 mg. The firm has also submitted *in vitro* dissolution data and a waiver request.

Introduction

Enalapril is a prodrug that is not highly active and, therefore must be hydrolyzed by hepatic esterases to produce its active metabolite, enalaprilat. Enalapril is rapidly absorbed orally and has an oral bioavailability of about 60% (not reduced by food). Although, peak plasma levels are attained within 1 hour, enalaprilat concentrations do not peak until 3 - 4 hours. Enalapril has a half-life of 1.3 hours but enalaprilat has a plasma half-life of about 11 hours because of its strong binding to the angiotensin-converting enzyme (ACE). The drug is eliminated mostly via the kidney either in its parent or metabolite form. Enalapril is indicated for the treatment of hypertension and congestive heart failure. Hydrochlorothiazide is not metabolized and is excreted unchanged in the urine. Its half-life ranges from 6-15 hours and more than 60% of the drug is eliminated within 24 hours.

The bioavailability of the individual drug is not affected when given as a combination product. Therefore, the combination product is reported to be bioequivalent to concomitant administration of the individual agents.

The reference listed drug is Merck's Vaseretic^{R} Tablets, 10 mg/25 mg.

I. Single-dose Bioequivalence Study Under Fasting Conditions (Study #:

A. Study Information:

Protocol #:
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: AAI Clinic, Chapel Hill, NC
Analytical Site:
Principal Investigator: Ralph Scallion, EE, MD
Study Dates: March 10 - 28, 2000
Analysis Dates: April 5 - May 11, 2000 (Enalapril and Enalaprilat)
March 29 - May 3, 2000 (HCTZ)
Study Design: Randomized, 2-way cross-over study with washout period of 14 days.
Randomization Scheme:

Sequence Number	Subject Numbers	Period 1	Period 2
1	3,4,5,6,7,9,10, 11, 12, 14,19, 24, 26, 28, 30, 31, 32,34, 36	A	B
2	1,2,8,13,15,16 17, 18,20,21, 22,23, 25,27, 29,33,35	B	A

A = Merck Vaseretic®
B =Cheminor Enalapril-Hydrochlorothiazide

Treatments: A: Enalapril-Hydrochlorothiazide, (10mg/25mg) Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99; Lot size: ; : 99.4%(enalapril), 99.0% (HCTZ); Content Uniformity: 101.2%(enalapril) 100.3%(hydrochlorothiazide)

B: Vaseretic®, (10mg/25mg) Tablets; Merck; Lot # J4897; Expiry Date: 01/01; Assay: 98.3%(enalapril) 98.7%(HCTZ); Content Uniformity: 97.6%(enalapril), 99.2%(HCTZ)

Formulation of Test Drug: Table 1

Subjects: 36 non-smoking male subjects were enrolled per protocol.

Housing: From the evening prior to dosing until after 36 hour blood draw.

Dosing: After 10-hour fast, with 240 ml water. Standard meals given at 4 hours after dosing.

Sampling Times: Blood samples (2 × 7 mL) collected at 0 h (pre-dose), 0.167, 0.333, 0.667,1, 1.5,2.0,2.5,3,4,6,9,12,16, 24, 36, 48, and 72 h

B. Study Results:

1. CLINICAL:

Drop-outs: None.

Adverse Events: A total of 9 medical adverse events were experienced by 7 subjects during the study. The adverse events include headache (4), lightheadedness (2), arm tingling (1), corneal abrasion (1) and fracture of the finger (1).

Protocol Deviations: There were 11 blood draw deviations involving 7 subjects. Blood draws were delayed mostly by $\leq$ 3 minutes.

2. ANALYTICAL METHODOLOGY:

Method:

Internal Standards: de

Sensitivity (LOQ): 0.25 ng/mL (enalapril)
0.50 ng/mL (enalaprilat)
2.50 ng/mL (hydrochlorothiazide)

Specificity: No interfering peaks at retention times of enalapril, enalaprilat, hydrochlorothiazide and their internal standards.

Linearity: Standard Curve Range:
0.25 - 250.0 ng/mL (Enalapril)
0.50 - 250.0 ng/mL (Enalaprilat)
2.50 - 300.0 ng/mL (HCTZ)
Correlation Coefficients:
Enalapril $\geq$ 0.98701
Enalaprilat $\geq$ 0.98190
Hydrochlorothiazide $\geq$ 0.99831

Quality Control Samples:
0.40, 20.0, and 200.00 ng/mL(enalapril)
0.80, 20.0, and 200.00 ng/mL(enalaprilat)
4.00, 40.0, and 200.0 ng/mL(HCTZ)

Regression: linear-weighted (1/concentration)

Accuracy:

[Enalapril]
Standard: 97.2 - 103.4%
QC Samples: 99.7 - 107.5%

[Enalaprilat]
Standard: 91.7 - 107.1%
QC Samples: 98.1 - 104.5%

[Hydrochlorothiazide]
Standard: 96.1 - 102.5%
QC Samples: 99.7 - 101.3%

Precision:

[Enalapril]
Standard: 4.0 - 9.5%
QC Samples: 6.2 - 10.5%

[Enalaprilat]
Standard: 3.1 - 7.1%
QC Samples: 7.9 - 10.6%

[Hydrochlorothiazide]
Standard: 1.1 - 4.8%
QC Samples: 2.2 - 6.6%

Reassays: A total of 34 and 73 samples were reanalyzed for enalapril and enalaprilat, respectively (13 samples for each analyte due to inconsistencies in PK profile and the remaining 21 enalapril and 60 enalaprilat samples due to poor chromatograms. A total of 21 samples were reanalyzed for hydrochlorothiazide (13 samples were from subject #11). An interference close to HCTZ peak and not baseline separated was the reason for reanalysis in subject #11 and since the reanalysis confirmed the first measurement, the interference was concluded to be an inherent artifact of the samples from subject #11. Therefore, no values were reported for subject 11 from the 13 samples. For the remaining 8 samples for HCTZ and all the samples for enalapril and enalaprilat, the reassays were accepted as the final results.

The firm has provided the following pre-study method validation results for both fasting and non-fasting studies:

Linearity:

[Enalapril]
Standard Curve Range:
0.25 - 500.0 ng/mL
QC Sample:
0.300,30.0,300 ng/mL
Correlation Coefficient: $\geq$ 0.99778

[Enalaprilat]
Standard Curve Range:
0.25 - 500.0 ng/mL
QC Sample:
0.300, 30.0, 300 ng/mL
Correlation Coefficient: $\geq$ 0.99783

[Hydrochlorothiazide]
Standard Curve Range:
1.0 - 150.0 ng/mL

QC Sample:
3.0, 30.0, 120 ng/mL
Correlation Coefficient: $\geq$ 0.99975

Accuracy:

[Enalapril]
INTER-DAY
Standard: 94.2 - 115.9%
QC Samples: 96.5 - 102.9%

INTRA-DAY
QC Samples: 97.5 - 110.0%

[Enalaprilat]
INTER-DAY
Standard: 94.9 - 112.5%
QC Samples: 99.5 - 106.1%

INTRA-DAY
QC Samples: 97.3 - 111.3%

[Hydrochlorothiazide]
INTER-DAY
Standard: 99.2 - 102.8%
QC Samples: 96.9 - 99.5%

INTRA-DAY
QC Samples: 98.7 - 98.9%

Precision:

[Enalapril]
INTER-DAY
Standard: 1.8 - 10.7%
QC Samples: 9.2 - 12.5%

INTRA-DAY
QC Samples: 4.0 - 6.1%

[Enalaprilat]
INTER-DAY
Standard: 1.7 - 10.4%
QC Samples: 3.9 - 10.7%

INTRA-DAY
QC Samples: 1.8 - 6.8%

[Hydrochlorothiazide]

INTER-DAY

Standard:	0.61 - 5.4%
QC Samples:	1.57 - 3.58%

INTRA-DAY

QC Samples:	0.76 - 1.81%

Specificity: no interference from endogenous compounds noted in plasma blanks or pre-dose subject plasma samples.

Recovery:

[Enalapril]

0.30 ng/mL	78% (10.9 %CV)
30.0 ng/mL	50% (4.1 %CV)
300.0 ng/mL	52% (4.5 %CV)
Quinapril(IS)	71.4%

[Enalaprilat]

0.30 ng/mL	89% (14.5 %CV)
30.0 ng/mL	85% (4.0 %CV)
300.0 ng/mL	93% (7.6 %CV)
Quinaprilat (IS)	64.3%

[Hydrochlorothiazide]

20 ng/mL	86.5%
200 ng/mL	85.1%
2000 ng/mL	81.5%
Chlorothiazide(IS)	63.5%

Stability:

[ENALAPRIL and ENALAPRILAT]

a) Stored Frozen at - 20°C: stable for 1185 days.
Note: Study samples stored for less than 52 days.

b) Freeze/Thaw: Stable over 3 cycles.

c) In-process: stable for 24 hours at room temp.

d) Refrigerator (5 °C): for 5 days

e) Autosampler: stable for 24 hours.

[HYDROCHLOROTHIAZIDE]

a) Stored Frozen at - 20°C: stable for 372 days.
   Note: Study samples stored for less than 44 days.
b) Freeze/Thaw: Stable over 3 cycles.
c) In-process: stable for 48 hours at room temp.
d) Refrigerator (5 °C): for 48 hours
e) Autosampler: stable for 24 hours.

Conclusion: Assay validation is acceptable.

3. PHARMACOKINETIC / STATISTICAL ANALYSES:

Enalapril:

Mean Plasma Concentrations: Table 2; Figure 1
Pharmacokinetic Parameters: Table 5

90% Confidence Intervals:	$LAUC_{0\text{-}72h}$	- 94.3 - 109.2%
	$LAUC_{0\text{-}INF}$	- 95.7 - 111.7%
	LC_{MAX}	- 97.1 - 121.6%
Test/Reference Ratio:	$AUC_{0\text{-}72h}$	1.00(0.92 - 0.95)
	$AUC_{0\text{-}INF}$	1.01(0.79 - 0.94)
	C_{MAX}	1.06(0.91 - 2.73)
$AUC_{0\text{-}72h}/AUC_{0\text{-}INF}$ Ratio:	Test	0.98(0.98 - 1.00)
	Reference	0.99(0.85 - 0.99)

Enalaprilat:

Mean Plasma Concentrations: Table 3; Figure 2
Pharmacokinetic Parameters: Table 6

90% Confidence Intervals:	$LAUC_{0\text{-}72h}$	- 94.9 - 110.1%
	$LAUC_{0\text{-}INF}$	- 95.7 - 111.1%
	LC_{MAX}	- 93.1 - 122.6%
Test/Reference Ratio:	$AUC_{0\text{-}72h}$	1.02(0.91 - 1.23)
	$AUC_{0\text{-}INF}$	1.01(0.94 - 1.20)
	C_{MAX}	1.06(0.84 - 2.06)

AUC_{0-72h}/AUC_{0-INF} Ratio:	Test	0.92(0.91 - 0.92)	
	Reference	0.91(0.88 - 0.95)	
Hydrochlorothiazide:			
Mean Plasma Concentrations:	Table 4; Figure 3		
Pharmacokinetic Parameters:	Table 7		
90% Confidence Intervals:	$LAUC_{0-72h}$	-	97.3 - 105.1%
	$LAUC_{0-INF}$	-	98.3 - 106.7%
	LC_{MAX}	-	96.0 - 113.5%
Test/Reference Ratio:	AUC_{0-72h}	1.01(1.01 - 1.02)	
	AUC_{0-INF}	1.01(1.05 - 1.08)	
	C_{MAX}	1.03(0.93 - 1.07)	
AUC_{0-72h}/AUC_{0-INF} Ratio:	Test	0.94(0.92 - 0.93)	
	Reference	0.94(0.92 - 0.95)	

Comments:

1. The maximum (mean) plasma concentrations for enalapril, enalaprilat and hydrochlorothiazide were attained at 1, 3 and 2 hours, respectively (Tables 2,3&4).

2. No subjects with zero-hour drug level, first scheduled post-dose time point as C_{max} or first measurable drug concentration as C_{max}. The reviewer recalculated the pharmacokinetic parameters and found them in complete agreement with those of the firm.

3. The reviewer's recalculated 90% confidence intervals for log-transformed AUCT, $AUC_{0-INF,}$ and C_{max} for enalapril, enalaprilat and hydrochlorothiazide corresponded with those of the firm and are all within the within acceptable limits.

4. The fasting study is complete.

II. Single-dose Bioavailability Study Under Non-Fasting Conditions (Protocol

A. Study Information:

Protocol #:	
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	AAI Clinic, Chapel Hill, NC

Analytical Site: [redacted]y

Principal Investigator: Ralph Scallion, EE, MD

Study Dates: March 3 - April 4, 2000

Analysis Dates: April 10 - May 9, 2000 (Enalapril and Enalaprilat)
April 4 - April 28, 2000 (HCTZ)

Study Design: Randomized, 3-way cross-over design with washout period of 14 days.

Randomization Scheme:

Sequence Number	Subject Numbers	Phase I	Phase II	Phase III
1	6, 7,20,21	A	B	C
2	1,2,11,24	B	C	A
3	10,15,17,18	C	A	B
4	5,9,12,13	C	B	A
5	4,16,19,23	B	A	C
6	3,8,14,22	A	C	B

A = Cheminor's enalapril/Hydrochlorothiazide (test, non-fasting)
B = Vaseretic® (reference, non-fasting)
C = Cheminor's enalapril/Hydrochlorothiazide (test, fasting)

Treatments:

A: Enalapril-Hydrochlorothiazide, (10mg/25mg) Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99 **(test, non-fasting)**

B: Vaseretic®, (10mg/25mg) Tablets; Merck; Lot # H4897; Expiry Date: 01/01 **(reference, non-fasting)**

C: Enalapril-Hydrochlorothiazide, (10mg/25mg)Tablets; Cheminor; Lot # E001B; Manufacturing Date: 10/99 **(test, fasting)**

Formulation of Test Drug: Table 1

Subjects: 24 non-smoking male subjects were enrolled per protocol.

Housing: At least 10 hours prior dosing until 36 hours blood draw.

Dosing:	Treatments A & B: Administered with 240mL water, 15 minutes after consuming a standard breakfast. Treatment C: Given with 240mL water after 10-hour fasting.
Sampling Times	Blood samples (2 × 7 mL) collected at 0 h (pre-dose), 0.167, 0.333, 0.667,1, 1.5,2.0,2.5,3,4,6,9,12,16, 24, 36, 48, and 72 h

B. Study Results:

1. CLINICAL:

Drop-outs:	A total of 4 subjects dropped out. In period II, subjects #5 and #7 were dropped due to failure to return to clinic. Subjects #9 and #14 withdrew after completing period I due to personal reasons. Therefore, 20 subjects completed the study.
Adverse Events:	A total of 7 adverse events occurring in 5 subjects were reported. These include headache (2), lightheadedness (1), nausea (1), hematoma (1), fever (1) and sore throat (1). Hematoma, fever and sore throat were considered not to be treatment-related. All were mild or moderate in nature and not definitely drug-related. The events appeared to occur evenly in both the test and reference products and resolved without pharmacologic treatment.
Protocol Deviations:	There were 10 deviations in blood collection times involving 7 subjects. Blood sampling delays were mostly $\leq$ 1 minute with the exceptions of Subjects #23 and 15 who had 61- and 270- minute delays, respectively. None of the subjects violated inclusion /exclusion criteria or took concomitant medications during the study.

2. ANALYTICAL METHODOLOGY:

Method:

Internal Standards:

Sensitivity (LOQ): 0.25 ng/mL (enalapril)
0.50 ng/mL (enalaprilat)
2.50 ng/mL (hydrochlorothiazide)

Specificity: No interfering peaks at retention times of enalapril, enalaprilat, hydrochlorothiazide and their internal standards.

Linearity: Standard Curve Range:
0.25 - 250.0 ng/mL (Enalapril)
0.50 - 250.0 ng/mL (Enalaprilat)
2.50 - 300.0 ng/mL (HCTZ)

Correlation Coefficients:
Enalapril $\geq$ 0.99566
Enalaprilat $\geq$ 0.99126
Hydrochlorothiazide $\geq$ 0.99851

Quality Control Samples:
0.40, 20.0, and 200.00 ng/mL(enalapril)
0.80, 20.0, and 200.00 ng/mL(enalaprilat)
4.00, 40.0, and 200.0 ng/mL(HCTZ)

Regression: linear-weighted (1/concentration)

Accuracy:

[Enalapril]
Standard: 96.2 - 102.4%
QC Samples: 99.7 - 103.2%

[Enalaprilat]
Standard: 94.8 - 104.0%
QC Samples: 99.9 - 101.9%

[Hydrochlorothiazide]
Standard: 95.5 - 102.1%
QC Samples: 99.6 - 102.6%

Precision:

[Enalapril]
Standard: 1.8 - 4.8%
QC Samples: 4.5 - 10.7%

[Enalaprilat]

Standard:	2.1 - 5.7%
QC Samples:	3.5 - 4.9%

[Hydrochlorothiazide]

Standard:	1.4 - 6.5%
QC Samples:	4.8 - 5.9%

Reassays: A total of 17 samples were reanalyzed for both enalapril and enalaprilat (5 and 7 samples for enalapril and enalaprilat, respectively, due to poor chromatograms; 6 and 3 samples for enalapril and enalaprilat, respectively, for irregular concentration value; 4 and 2 samples for enalapril and enalaprilat, respectively, for below LOQ; 1sample for both enalapril and enalaprilat due to "lost sample", and 1 and 4 samples for enalapril and enalaprilat, respectively, because established criteria despite of acceptable value. A total of 26 samples were reanalyzed for hydrochlorothiazide (14 due to "chromotogram not evaluable", 10 due to "irregular concentration value", 1 for "above upper limit concentration value," and 1 because "lost sample"). Additional 18 samples from subject #10 were reinjected because of interference peak was not separated from HCTZ at first injection. The values of last repeats or the mean values of repeats that are similar in value were reported as final results.

Conclusion: Assay is acceptable.

3. **PHARMACOKINETIC / STATISTICAL ANALYSES:**

Enalapril:

Mean Plasma Concentrations: Table 8; Figure 4

Pharmacokinetic Parameters: Table 11

Test-fed/Ref. Fed Ratio:	$AUC_{0\text{-}72h}$	0.95(0.95 - 1.10)
	$AUC_{0\text{-}INF}$	0.94(0.95 - 1.12)
	C_{MAX}	1.09(0.68 - 1.09)
$AUC_{0\text{-}72h}/AUC_{0\text{-}INF}$ Ratio:	Test Fasting	0.98(0.99-1.00)
	Test Non-fasting	0.99(0.98-0.99)
	Ref. Non-fasting	0.98(0.98-0.99)

Enalaprilat:

Mean Plasma Concentrations: Table 9; Figure 5
Pharmacokinetic Parameters: Table 12

Test-fed/Ref. Fed Ratio:	$AUC_{0\text{-}72h}$	0.96(0.76 - 084)
	$AUC_{0\text{-}INF}$	0.97(0.79 - 0.80)
	C_{MAX}	0.93(0.60 - 1.11)

$AUC_{0\text{-}72h}/AUC_{0\text{-}INF}$ Ratio:	Test Fasting	0.93(0.88-0.94)
	Test Non-fasting	0.93(0.90-0.93)
	Ref. Non-fasting	0.91(0.88-0.95)

Hydrochlorothiazide:

Mean Plasma Concentrations: Table 10; Figure 6
Pharmacokinetic Parameters: Table 13

Test-fed/Ref. Fed Ratio:	$AUC_{0\text{-}72h}$	0.92(0.89 - 0.90)
	$AUC_{0\text{-}INF}$	0.93(0.88 - 0.91)
	C_{MAX}	0.99(0.92 - 1.08)

$AUC_{0\text{-}72h}/AUC_{0\text{-}INF}$ Ratio:	Test Fasting	0.94(0.91-0.96)
	Test Non-fasting	0.94(0.92-0.96)
	Ref. Non-fasting	0.95(0.97-0.98)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means and found them in complete agreement with those of the firm.

2. No subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug level as C_{max}. Subjects # 6 and #19 had zero-hour (predose) enalapril levels but were not dropped. The reviewer agrees with this decision since the levels were < 5% of the respective Cmax values of the subjects.

3. Ratio of the means for $AUC_{0\text{-}72h}$, $AUC_{0\text{-}INF}$, and C_{max} between test (non-fasting) and reference (non-fasting) are within acceptable limits.

4. The non-fasting study is complete.

In Vitro Dissolution Testing and Waiver Request:

The firm has conducted dissolution testing on its 5 mg/12.5 mg and 10 mg/25 mg tablets of both the test and reference products, using the current USP method and is requesting waivers of the in-vivo bioequivalence study requirements for its 5 mg/12.5 mg tablet per 21 CFR 320.22(d)(2), based on an acceptable in-vivo bioequivalence study on the 10 mg/25 mg strength, similarly proportional formulations as listed in Table 1. The comparative dissolution data and testing conditions are presented in Table 14.

Comments:

1. The test and reference products used in the dissolution testing and biostudies were from same lots.

2. The following f_2 **comparisons** were performed:

	Test 5mg/12.5mg	Test 10mg /25 mg	Ref. 5mg/ 12.5mg	Ref. 10mg /25 mg
Test 5mg/12.5mg	- / -	66 / 67	54/50	62 / 48
Test 10mg/25 mg	66 / 67	- / -	71 / 51	82 / 57
Ref. 5mg/12.5mg	54/50	71/51	- / -	77 / 55
Ref. 10mg/25 mg	62 / 48	82 / 57	77 / 55	- / -

Recommendations:

I. The *in vivo* bioequivalence study conducted under fasting conditions by Cheminor, on its Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, lot #E001B, comparing it to the reference product, Vaseretic[R] tablets, 10 mg/25mg, lot # J4897, by Merck & Co., is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, is bioequivalent to the reference product, Vaseretic[R] tablets, 10 mg/25mg, manufactured by Merck & Co.

II. The *in vivo* bioavailability study conducted under non-fasting conditions by Cheminor, Inc. on its Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, lot #E001B, comparing it to the reference product, Vaseretic[R] tablets, 10 mg/25 mg, lot # J4897, by Merck & Co., is acceptable to the Division of Bioequivalence. The study demonstrates that Cheminor's Enalapril Maleate Hydrochlorothiazide tablets, 10 mg/25 mg, is bioequivalent to the reference product, Vaseretic[R] tablets, 10 mg/25mg, manufactured by Merck & Co.

III. The *in vitro* dissolution testing submitted by the firm on its Enalapril Maleate-Hydrochlorothiazide (5 mg/12.5 mg and 10 mg/ 25 mg) tablets is acceptable. The formulation for 5 mg/12.5 mg, test tablets is proportionally similar to the 10 mg/25 mg strength of the test product which underwent bioequivalence testing. The waiver of the *in vivo* bioequivalence study requirements for 5 mg /12.5 mg of the test product can be granted under 21 CFR 320.22(d)(2). The 5 mg/12.5 mg test tablets are therefore deemed bioequivalent to the 5 mg/12.5 mg tablets of Vaseretic® manufactured by Merck & Co.

IV. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution should be conducted in 900 mL Water using USP Apparatus II(Paddle) at 50 rpm. The test product should meet the following specifications:

Enalapril -	in 30 minutes
Hydrochlorothiazide -	in 30 minutes

V. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

9/20/2000

Patrick Nwakama, Pharm.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 9/21/2000

Concur: _____ Date 9/29/00
for Dale P. Conner,Pharm.D.
Director
Division of Bioequivalence

TABLE 2

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
ARITHMETIC MEAN ENALAPRIL PLASMA LEVELS (ng/mL) Vs TIME (n= 36)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV %)	0.00	(CV%)	.
0.17	1.13	162.29	1.1073	116.62	1.02
0.33	16.20	91.82	15.00	104.12	1.08
0.67	75.81	36.29	68.79	46.35	1.10
1.00	83.12	26.26	77.27	36.52	1.07
1.50	54.74	37.47	54.65	37.06	1.00
2.00	33.50	40.13	33.76	40.39	0.99
2.50	20.57	39.68	21.07	41.50	0.98
3.00	12.35	37.79	12.77	38.33	0.97
4.00	5.77	37.17	6.09	42.72	0.95
6.00	1.96	40.21	2.18	61.63	0.90
9.00	0.65	55.67	0.95	78.71	0.68
12.00	0.26	106.14	0.42	101.49	0.62
16.00	0.05	287.85	0.15	185.55	0.33
24.00	0.00	-	0.04	376.74	0.00
36.00	0.00	-	0.00	0.00	0.00
48.00	0.00	-	0.00	0.00	0.00
72.00	0.00	-	0.00	0.00	0.00

TABLE 3

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEAN ENALAPRILAT PLASMA LEVELS (ng/mL) Vs TIME (n = 36)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV %)	0.00	(CV%)	.
0.17	0.03	600.00	0.09	460.29	0.33
0.33	0.12	310.93	0.18	251.91	0.67
0.67	2.10	115.72	1.70	70.34	1.23
1.00	7.63	121.24	6.24	110.00	1.22
1.50	20.46	76.03	21.35	85.44	0.96
2.00	35.63	53.91	34.11	58.50	1.04
2.50	45.10	43.66	42.56	51.53	1.06
3.00	49.33	43.13	46.71	43.34	1.06
4.00	48.90	38.23	45.07	36.61	1.08
6.00	33.82	32.38	33.90	34.01	1.00
9.00	20.27	30.71	19.96	28.71	1.02
12.00	11.12	28.68	11.18	33.15	0.99
16.00	5.41	32.03	5.71	33.73	0.95
24.00	2.81	31.33	2.88	35.25	0.97
36.00	1.52	22.74	1.53	28.78	0.99
48.00	1.16	26.72	1.13	31.34	1.03
72.00	0.71	49.55	0.70	48.06	1.01

TABLE 4

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEAN HYDROCHLOROTHIAZIDE PLASMA LEVELS (ng/mL) Vs TIME
(n = 36)

Time	Test Treatment A		Reference Treatment B		Ratio (A/B)
0	0.00	(CV %)	0.00	(CV%)	.
0.17	0.27	421.92	0.00	-	-
0.33	5.53	186.34	3.81	132.90	1.45
0.67	53.94	72.43	48.53	76.47	1.11
1.00	114.24	48.36	102.61	56.73	1.11
1.50	143.50	32.78	131.41	38.15	1.09
2.00	145.69	26.80	138.69	31.43	1.05
2.50	135.50	22.86	138.10	28.12	0.98
3.00	122.69	21.48	125.34	23.96	0.98
4.00	99.63	20.42	101.48	21.55	0.98
6.00	61.05	23.30	61.85	24.21	0.99
9.00	38.64	22.02	40.28	28.09	0.96
12.00	25.13	22.57	25.42	23.93	0.99
16.00	17.01	25.08	17.07	24.41	0.99
24.00	11.02	29.35	10.72	25.11	1.03
36.00	5.17	47.93	4.70	37.45	1.10
48.00	1.71	116.51	1.63	116.78	1.05
72.00	0.15	412.55	0.18	412.23	0.83

TABLE 5

MEAN (%CV) ENALAPRIL PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 36)				
Parameter	Arithmetic Mean A = TEST Vaseretic®	Arithmetic Mean B = Vaseretic®	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	143.5 (37.0)	142.5(41.8)	1.01	94.3% - 109.2%
AUCI (ng x hr/mL)	145.7(38.4)	143.8 (41.2)	1.03	95.7% - 111.7%
CMAX (ng/mL)	89.1(22.6)	84.2(27.4)	1.09	97.1% - 121.6%
KEL (hr^{-1})	0.39 (0.16)	0.33 (0.16)	-----	-----
THALF (hr)	2.08 (0.85)	2.65 (1.88)	-----	-----
TMAX (hr)	0.87 (0.20)	0.93 (0.29)	-----	-----

TABLE 6

MEAN (%CV) ENALAPRILAT PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 41)				
Parameter	Arithmetic Mean A = TEST	Arithmetic Mean B = Vaseretic®	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	455.9 (106.11)	447.8 (113.4)	1.02	94.9% - 110.1%
AUCI (ng x hr/mL)	497.4 (105.2)	492.7 (115.2)	1.03	95.7% - 111.1%
CMAX (ng/mL)	52.9 (21.1)	50.1 (21.3)	1.07	93.1% - 122.6%
KEL (hr^{-1})	0.02 (0.01)	0.03 (0.01)	-----	-----
THALF (hr)	32.6 (12.8)	31.7 (11.4)	-----	-----
TMAX (hr)	3.50 (0.86)	3.31 (0.81)	-----	-----

*Ratio (A/B) = e [LSMEAN of Ln A - LSMEAN of Ln B]

**Used natural Log Transformed Parameter

TABLE 7

MEAN (%CV) HYDROCHLOROTHIAZIDE PHARMACOKINETIC PARAMETERS FOLLOWING 10 MG/25 MG (1 X 10 MG/25 MG) DOSE OF ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE TABLETS UNDER FASTING CONDITIONS (n = 36)				
Parameter	Arithmetic Mean A = Vaseretic®	Arithmetic Mean B = TEST	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUCT (ng x hr/mL)	1150.7 (236.6)	1141.92 (251.8)	1.01	97.3% - 105.1%
AUCI (ng x hr/mL)	1127.9 (250.4)	1213.8 (265.3)	1.02	98.3% - 106.7%
CMAX (ng/mL)	162.3 (39.9)	157.14(43.5)	1.04	96.0% - 113.5%
KEL (hr^{-1})	0.06 (0.01)	0.06 (0.01)	-----	-----
THALF (hr)	13.3 (9.1)	11.54 (3.47)	-----	-----
TMAX (hr)	1.86(0.69)	2.1(0.75)	-----	-----

*Ratio (A/B) = e [LSMEAN of LNA - LSMEAN of LNB]

**Used natural Log Transformed Parameter

TABLE 8

ARITHMETIC MEAN ENALAPRIL PLASMA LEVELS [ng/mL] Vs TIME IN NON-FASTING STUDY
(n = 20)

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.04 (435.89%)	0.01 (447.21%)	0.00	-	4.00
0.17	0.33 (207.53%)	0.13 (273.31%)	1.35 (192.16%)	0.24	2.54
0.33	4.04 (189.49%)	1.94 (119.21%)	19.08 (89.74%)	0.21	2.08
0.67	21.81 (78.16%)	14.26 (84.48%)	63.80 (53.50%)	0.34	1.53
1.00	38.85 (57.73%)	29.72 (69.88%)	65.39 (43.11%)	0.59	1.31
1.5	35.30 (47.37%)	37.19 (43.64%)	43.41 (33.75%)	0.81	0.95
2.0	24.39 (52.49%)	31.43 (42.19%)	25.91 (34.39%)	0.94	0.78
2.5	17.73 (75.33%)	21.45 (44.40%)	17.13 (47.44%)	1.03	0.83
3.0	11.87 (87.18%)	14.47 (61.97%)	10.15 (61.65%)	1.17	0.82
4.0	5.20 (79.05%)	6.64 (63.08%)	4.78 (55.46%)	1.09	0.78
6.0	1.19 (47.76%)	1.43 (40.07%)	1.44 (68.51%)	0.83	0.83
9.0	0.34 (61.82%)	0.43 (47.98%)	0.40 (70.70%)	0.85	0.79
12.0	0.09 (179.50%)	0.14 (134.66%%)	0.12 (144.84%)	0.75	0.64
16.0	0.02 (447.21%)	0.03 (307.87%)	0.01 (447.21%)	2.00	0.66
24.0	0.00	0.00	0.00	-	-
36.0	0.00	0.00	0.00	-	-
48.0	0.00	0.02 (447.21%)	0.00	-	-
72.0	0.00	0.00	0.02 (447.21%)	0.00	-

TABLE 9

ARITHMETIC MEAN ENALAPRILAT PLASMA LEVELS [ng/mL] VS TIME IN NON-FASTING STUDY
(n = 20)

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.00	0.00	0.00	-	-
0.17	0.00	0.00	0.00	-	-
0.33	0.00	0.00	0.00	-	-
0.67	0.20 (191.07%)	0.06 (308.90%)	1.02 (81.76%)	0.20	3.33
1.00	1.03 (136.95%)	0.58 (119.24%)	4.80 (96.62%)	0.21	1.77
1.5	4.45 (166.22%)	2.59 (120.10%)	17.69 (74.02%)	0.25	1.72
2.0	10.09 (110.79%)	6.51 (103.01%)	29.94 (49.69%)	0.34	1.55
2.5	15.05 (80.14%)	12.41 (73.35%)	37.45 (40.98%)	0.40	1.21
3.0	20.08 (64.37%)	18.83 (50.73%)	41.76 (36.15%)	0.48	1.21
4.0	25.43 (42.07%)	27.40 (42.27%)	43.71 (26.99%)	0.58	0.93
6.0	21.88 (35.78%)	23.61 (39.32%)	30.32 (25.14%)	0.72	0.93
9.0	14.51 (36.52%)	16.32 (44.84%)	19.46 (28.93%)	0.75	0.89
12.0	9.22 (39.10%)	9.61 (39.03%)	11.04 (36.49%)	0.84	0.96
16.0	4.83 (48.09%)	5.24 (46.37%)	5.69 (49.49%)	0.85	0.92
24.0	2.50 (42.04%)	2.57 (35.83%)	2.61 (39.83%)	0.96	0.97
36.0	1.37 (27.28%)	1.33 (28.15%)	1.38 (30.52%)	0.99	1.03
48.0	1.02 (33.98%)	1.00 (35.42%)	0.97 (34.41%)	1.05	1.02
72.0	0.71 (32.96%)	0.68 (33.13%)	0.64 (41.75%)	1.11	1.04

TABLE 10

ARITHMETIC MEAN HYDROCHLOROTHIAZIDE PLASMA LEVELS (ng/mL) VS TIME IN NON-FASTING STUDY
(n = 20)

Time (Hours)	Non-Fasting Test Treatment A Mean (CV%)	Non-Fasting Reference Treatment B Mean (CV%)	Fasting Test Treatment C Mean (CV%)	Ratio (A/C)	Ratio (A/B)
0	0.00	0.00	0.00	0.00	0.00
0.17	0.00	0.00	0.57 (447.21%)	-	0.00
0.33	5.46 (301.44%)	0.48 (320.33%)	8.79 (159.49%)	0.62	11.37
0.67	29.59 (128.74%)	13.93 (110.14%)	58.36 (77.85%)	0.51	2.12
1.00	64.02 (65.28%)	48.83 (91.82%)	118.42 (52.98%)	0.54	1.31
1.5	102.76 (36.57%)	86.59 (67.90%)	158.86 (46.44%)	0.65	1.19
2.0	117.62 (29.77%)	111.02 (44.32%)	154.53 (33.13%)	0.76	1.06
2.5	115.59 (24.23%)	120.03 (31.39%)	146.01 (23.84%)	0.79	0.96
3.0	111.91 (30.18%)	116.22 (20.91%)	129.74 (23.50%)	0.86	0.96
4.0	95.30 (34.59%)	105.01(20.97%)	105.42 (20.89%)	0.90	0.91
6.0	58.29 (32.40%)	69.13 (26.01%)	63.58 (27.17%)	0.92	0.89
9.0	36.10 (30.03%)	40.73 (23.57%)	40.22 (23.68)	0.90	0.89
12.0	25.06 (31.58%)	27.13 (22.83%)	27.55 (22.87%)	0.91	0.92
16.0	16.13 (29.88%)	17.83 (24.86%)	18.56 (24.82%)	0.87	0.90
24.0	10.08 (31.02%)	11.31 (30.41%)	11.78 (27.28%)	0.86	0.89
36.0	4.41 54.28%)	4.73 (51.21%)	5.11 (50.91%)	0.86	0.93
48.0	1.63 (115.20%)	1.58 (114.94%)	2.05 (106.29%)	0.79	1.03
72.0	0.00	0.00	0.13 (447.21%)	-	0.00

TABLE 11

MEAN ENALAPRIL PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL 10 MG/25 MG (1 X 10 MG/25 MG) DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	83.7 (25.4)	88.5 (25.4)	116.2 (41.0)	0.95
AUCI (ng x hr/mL)	84.6 (25.6)	89.9 (25.9)	118.7 (41.5)	0.94
CMAX (ng/mL)	50.5(15.6)	45.4 (12.9)	72.7 (30.0)	1.09
KEL (hr^{-1})	0.54 (0.23)	0.48 (0.26)	0.52 (0.23)	-----
THALF (hr)	1.70 (1.25)	1.90 (1.07)	1.62 (0.74)	-----
TMAX (hr)	1.23 (0.43)	1.52 (0.62)	0.83 (0.22)	-----

* Ratio (A/B) = $e^{[\text{LSMEAN of Ln A - LSMEAN of Ln B}]}$

TABLE 12

MEAN ENALAPRILAT PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL DOSE 10 MG/25 MG DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	295.9 (85.3)	307.1 (99.9)	162 (42.2)	0.96
AUCI (ng x hr/mL)	335.2 (89.2)	337.2 (100.8)	169 (41.8)	0.97
CMAX (ng/mL)	26.7 (11.6)	28.2(11.7)	101 (38.2)	0.93
KEL (hr^{-1})	0.02 (0.01)	0.02 (0.01)	0.60 (50.6)	-----
THALF (hr)	36.2 (11.2)	32.5 (8.1)	1.55 (62.0)	-----
TMAX (hr)	4.2 (1.2)	4.6 (0.94)	1.01 (34.3)	-----

* Ratio (A/B) = $e^{[\text{LSMEAN of Ln A - LSMEAN of Ln B}]}$

TABLE 13

MEAN HYDROCHLOROTHIAZIDE PHARMACOKINETIC PARAMETERS FOLLOWING A SINGLE ORAL DOSE 10 MG/25 MG DOSE IN A FOOD STUDY (n = 20)				
Parameter	Arithmetic Mean A = TEST (Fed)	Arithmetic Mean B = REF (Fed)	Arithmetic Mean C = TEST (Fasting)	LSMEANS* Ratio (A/B)
AUCT (ng x hr/mL)	1020.2 (274.05)	1090.1 (233.9)	1220.7 (262.2)	0.92
AUCI(ng x hr/mL)	1084.0 (274.2)	1148.9 (237.3)	1292.9 (276.7)	0.93
CMAX (ng/mL)	137.1 (29.2)	137.7 (33.1)	181.5 (60.2)	0.99
KEL (hr^{-1})	0.07 (0.02)	0.07 (0.02)	0.06 (0.02)	-----
THALF (hr)	11.2 (2.7)	10.53 (2.5)	11.3 (3.06)	-----
TMAX (hr)	1.93 (0.67)	2.42 (0.78)	2.22 (1.25)	-----

* Ratio (A/B) = $e^{[\text{LSMEAN of Ln A} - \text{LSMEAN of Ln B}]}$

TABLE 14

IN-VITRO DISSOLUTION TESTING

Drug: Enalapril Maleate and Hydrochlorothiazide Tablets Dose Strength(s): 5 mg/12.5 mg and 10 mg/25 mg ANDA #: 75-909 Firm: Cheminor Drugs Ltd. Submission Date: June 16, 2000 File Name: 75-909SDW.600						
I. Conditions for Dissolution/Release Testing: USP METHOD						
USP XXIV Apparatus: Type 2 (Paddles) RPM: 50 No. Units Tested: 12 Reference Drug: Vaseretic®				Media: Water at 37°C Volume: 900 mL Tolerance: in 30 min(enalapril) Tolerance: in 30 min(Hydrochlorothiazide) Assay Method:		
II. Results of In Vitro Dissolution/Release Testing: [ENALAPRIL COMPONENT]						
Sampling Times (min)	Test Product: Enalapril Maleate/HCTZ Tablets Lot No.: E001A Strength: 5 mg/12.5 mg			Reference Product: Vaseretic® Tablets Lot No.: J4944 Strength: 5 mg/12.5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	79.0		17.0	95.0		2.9
20	95.0		6.2	97.0		1.4
30	98.0		3.4	98.0		1.1
45	99.0	94.0 - 0-	1.9	99.0		1.2
Sampling Times (min)	Test Product: Enalapril Maleate /HCTZ Tablets Lot No.: E001B Strength: 10 mg/25 mg			Reference Product: Vaseretic® Tablets Lot No.: J4897 Strength: 10 mg /25 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	88.0		15.2	90.0		5.1
20	97.0		6.9	97.0		1.5
30	99.0		3.2	97.0		1.3
45	100.0	98.0	1.3	97.0		0.9

II. Results of In Vitro Dissolution/Release **Testing:[HYDROCHLOROTHIAZIDE]**						
Sampling Times (min)	Test Product: Enalapril Maleate/HCTZ Tablets Lot No.: E001A Strength: 5 mg/12.5 mg			Reference Product: Vaseretic® Tablets Lot No.: J4944 Strength: 5 mg/12.5 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	57		16.9	70		6.2
20	89		9.5	85		3.4
30	97		6.0	88		2.7
45	100		4.6	89		2.5
Sampling Times (min)	Test Product: Enalapril Maleate /HCTZ Tablets Lot No.: E001B Strength: 10 mg/25 mg			Reference Product: Vaseretic® Tablets Lot No.: J4897 Strength: 10 mg /25 mg		
	Mean %	Range	CV%	Mean %	Range	CV%
10	65		12.8	78		4.9
20	92		9.2	93		2.7
30	99		6.3	96		2.0
45	102		4.1	97		1.7

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-909 APPLICANT: CHEMINOR DRUGS LTD.

DRUG PRODUCT: ENALAPRIL MALEATE /HYDROCHLOROTHIAZIDE TABLETS
5 mg/12.5 mg & 10 mg/25 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The dissolution testing should be incorporated into your stability and quality control programs as specified in USP XXIV.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Barbara Myers Davit
Dale P. Conner,Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research