

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
76175

BIOEQUIVALENCY REVIEW(S)

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-175

SPONSOR : Geneva PTC

DRUG AND DOSAGE FORM : Mefloquine Hydrochloride Tablets

STRENGTH(S) : 250 mg

TYPES OF STUDIES :

SD

SDF

MULT

OTHER

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : In single dose fasting and post-prandial bioequivalence studies, Mefloquine Hydrochloride tablets, 250 mg were shown to be bioequivalent to Lariam® tablets, 250 mg.

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

| Inspection needed: YES / <input type="checkbox"/> NO | Inspection status: | Inspection results: |
|---|------------------------------|---------------------|
| First Generic _____ | Inspection requested: (date) | |
| New facility _____ | Inspection completed: (date) | |
| For cause _____ | | |
| Other _____ | | |

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : MSH DATE : 7/20/01

for TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 7/20/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

for INITIAL : DP / IS DATE : 7/31/2001

Mefloquine Hydrochloride Tablets
250 mg
ANDA #76-175
Reviewer: Mamata Gokhale

Geneva PTC
2400 Route 130 North
U.S. Agent: Ranbaxy
Dayton NJ 08810
Submission Date: 5/23/01

Review of Bioequivalence Studies and Dissolution Data

I. Introduction

Indication: Schizonticidal agent indicated for the treatment and prophylaxis of malaria.

Type of Submission: ANDA for 250 mg strength of Mefloquine HCl Tablets.

Contents of Submission: Single dose fasting and post-prandial bioequivalence studies and dissolution data.

RLD: Lariam® Tablets, 250 mg, manufactured by Roche Laboratories.

Recommended dose: For the treatment of malaria in adults, five tablets (1250 mg) should be given as a single dose while in pediatric patients, two doses of 25 mg/kg should be given 6-8 hours apart. For malaria prophylaxis, one 250 mg Lariam® tablet once weekly is recommended.

II. Background

Mefloquine is 2-aryl substituted analog of quinine available as a racemic mixture. Following administration of single oral mefloquine doses of 250-1250 mg in healthy individuals, peak mefloquine concentrations in plasma are attained within 6-24 hours. Mefloquine hydrochloride is slowly absorbed from the GI tract and appears to undergo little, if any, first-pass elimination. The major metabolite (the 4-carboxylic acid derivative) of mefloquine appears to have no antimalarial activity. The absorption half-life is 0.36 to 2 hours. Mefloquine is slowly eliminated from the body. The terminal elimination half-life for mefloquine shows considerable interindividual variation, ranging from 15-33 days (mean: 21 days) in healthy adults. Limited evidence indicates that bioavailability of mefloquine is greater when the drug is administered with food than when administered in the fasting state. Labeling mentions that mefloquine hydrochloride should not be taken on an empty stomach.

The DBE has not reviewed any ANDA submissions on Mefloquine Tablets. This application is a potential first generic. For oral products with long half life, the CDER Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations, October 27, 2000, recommends that, a non-replicate single dose parallel design can be used for bioequivalence determination. In the parallel BE study, sample collection time should be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. The firm has submitted single dose single

period parallel design bioequivalence studies under fasting and fed conditions with adequate sampling times.

III. Single-dose Parallel Fasting Bioequivalence Study

A. Study Information

Study Number B-12099

Clinical Director

Clinical Site

Study Dates Study Group I: 4/21-8/11/00

Study Group II: 6/10-9/30/00

Analytical Site

Analytical Director

Analysis Dates 8/3-10/6/00

Sample Storage Period Up to 168 days

| | | |
|---|---|---|
| Treatment ID | A | B |
| Test or Reference | Test | Reference |
| Product Name | Mefloquine Hydrochloride | Lariam® |
| Manufacturer | Geneva PTC | Roche Laboratories |
| Lot No. | D000301 | 0171 |
| Manufacture Date | 3/00 | N/A |
| Expiration Date | N/A | 4/02 |
| Strength | 250 mg | 250 mg |
| Dosage Form | Tablets | Tablets |
| ANDA Batch Size | | N/A |
| Production Batch Size | | N/A |
| Potency (%) | 99.2 | 99.4 |
| Content Uniformity (mean, %cv, range, n) | 98.1, 0.4, 10 | 97.7, 1.7, 10 |
| Formulation | See Table #1 | N/A |
| Dose Administered | 750 mg (3 x 250 mg) | 750 mg (3 x 250 mg) |
| Route of Administration | Oral | Oral |
| Length of Fasting | 10 hours prior to dosing 4 hours post-dosing | 10 hours prior to dosing 4 hours post-dosing |
| No. of Sequences | 1 | Crossover N |
| No. of Periods | 1 | Replicate Design N |
| No. of Treatments | 2 | Balanced Y |
| No. of Groups (if appropriate) | 2 | Washout Period N/A |

| | |
|--|---|
| Randomization Scheme | A: 1, 4, 6, 8, 11, 16, 17, 19, 20, 22, 23, 25, 27, 28, 29, 32, 33, 35, 37, 39, 41, 44, 46, 47, 49, 52, 54, 58, 59, 60, 62, 63, 66, 67, 70 B: 2, 3, 5, 7, 9, 10, 12, 13, 14, 15, 18, 21, 24, 26, 30, 31, 34, 36, 38, 40, 42, 43, 45, 48, 50, 51, 53, 55, 56, 57, 61, 64, 65, 68, 69 |
| Blood Sampling Times | 0 (pre-mefloquine dose), 1, 5, 10, 15, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 44, 48, 72, 120, 168, 336, 672, 1008, 1344, 1680, 2016 and 2688 hours |
| Blood Volume Collected/Sample | 10 mL |
| Blood Sample Processing/Storage | EDTA plasma samples were stored at -20°C |
| IRB Approval | Y |
| Informed Consent | Y |
| No. Enrolled | 66 (Group I: #1 to #47 and Group II: #48 to #77) |
| No. Dosed | 66 (There were no subjects dosed for #'s 23, 26, 28, 38, 40, 53, 56, 59, 62 and 70) |
| No. Completing | 65 (32 for test, 33 for reference) |
| No. With Plasma Spls Analyzed | 65 |
| Length of Confinement | From 10 hours pre-dosing to 48 hours post-dosing. |
| Restrictions | Along with the standard dietary, activity and drug restrictions, the exclusion criteria included hypersensitivity to mefloquine or related drugs. |
| Safety Monitoring | Vital signs (blood pressure and heart rate) were monitored prior to dosing and at 6, 24, 36 and at each return visit. EKGs were recorded at 2, 6, 12, 36, 48 and 2688 hours. |
| Demographics (Study #B-12099) | |
| Age (Mean ± SD, Range) | 26.5 ± 8.4, 18-45 years |
| Groups < 18 | 0 |
| 18 - 40 | 59 (89.4%) |
| 40 - 64 | 7 (10.6%) |
| 65 - 75 | 0 |
| > 75 | 0 |
| Gender | 66 Males (100%) |
| Race | 57 Caucasians (86.4%), 6 African Americans (9.1%), 3 Asians (4.5%) |
| Height (Mean ± SD, Range) | 70.1 ± 2.4, 65-76 cm |
| Weight (Mean ± SD, Range) | 177.3 ± 15.0, 118-231 Kg |

B. Study Results

1. Clinical

Dropout Information

No. of Dropouts 1

Subjects No 47

Reason Subject #47 tested positive for Hepatitis B when screened for future study.

Period N/A

Adverse Events One remotely and fourteen possibly drug-related mild or moderate adverse events; eight occurred during treatment A and 7 occurred during treatment B. For additional information see pages 838-839, volume 1.2.

Protocol Deviations Minor deviations with respect to blood sampling times, food and concomitant medication restrictions; unlikely to compromise the integrity of the study. Actual sampling times were used for all calculations.

Comments: None

2. Analytical Method Validation

Comments: Analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Mefloquine

| | | |
|--|---|-------------|
| Mean Plasma Concentrations | Table #2, Figures #1 and 2 | |
| Mean Pharmacokinetic Parameters | Table #4 | |
| 90% Confidence Intervals | lnAUCt: 85.89-112.10 lnAUCi: 85.86-112.32 lnCmax: 84.55-103.01 Details in Table #5 | |
| AUCt/AUCi ratio | Test | Reference |
| Mean, %CV, range | 0.95, 1.92, | 0.95, 2.36, |

| Total standard deviation and root mean square error, ln-transformed PK data | | |
|---|------------|--------|
| Drug (parent) | Mefloquine | |
| PK parameter | lnCmax | lnAUCt |
| Root MSE, test & ref combined | 0.2384 | 0.3215 |

Comments: (on pharmacokinetic and statistical analyses)

1) For mefloquine, the Kel and AUCi values could not be determined for subjects #20 and 29 during treatment A (test).

2) In the pharmacokinetic analysis of mefloquine, subjects with

- a) measurable drug concentrations at 0 hour: None
- b) first scheduled post-dose sampling time as Tmax: None
- c) first measurable concentration as Cmax: None

3) The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.

4) The 90% confidence intervals for the log transformed AUCt, AUCi and Cmax are within the acceptable limits of 80-125%.

Conclusion: The single-dose parallel design fasting bioequivalence study is acceptable.

IV. Single-dose Parallel Design Post-Prandial Bioequivalence Study

A. Study Information

Study Number R00-724

Clinical Director

Clinical Site

Study Dates 12/16/00-2/23/01

Analytical Director

Analytical Site

Analysis Dates 3/3-3/30/01

Sample Storage Period Up to 105 days

| | | |
|--------------------------|--------------------------|--------------------|
| Treatment ID | A | B |
| Test or Reference | Test | Reference |
| Product Name | Mefloquine Hydrochloride | Lariam® |
| Manufacturer | Geneva PTC | Roche Laboratories |
| Lot No. | D000301 | 0171 |
| Dose Administered | 3x250 mg | 3x250 mg |

| Route of Administration | Oral | Oral |
|--|---|---|
| Length of Fasting | 10 hours pre-dosing 4.25 hours post-dosing | 10 hours pre-dosing 4.25 hours post-dosing |
| Food/Drug Interval | 30 minutes | 30 minutes |
| Standardized Breakfast | Y | Y |
| Breakfast Description | Standard high-fat | Standard high-fat |
| No. of Sequences | 1 | Crossover N |
| No. of Periods | 1 | Replicate Design N |
| No. of Treatments | 2 | Balanced Y |
| No. of Groups (if appropriate) | N/A | Washout Period N/A |
| Randomization Scheme | A: 1, 4, 7, 9, 12, 15, 17, 18, 24, 26, 29, 30, 31, 33, 35, 38, 39, 40, 41, 42, 44, 46, 47, 51, 53, 54, 55, 56, 57, 58, 60, 64, 65, 67, 68 B: 2, 3, 5, 6, 8, 10, 11, 13, 14, 16, 19, 20, 21, 22, 23, 25, 27, 28, 32, 34, 36, 37, 43, 45, 47, 48, 49, 52, 59, 61, 62, 63, 66, 69, 70 | |
| Blood Sampling Times | 0 (pre-mefloquine dose), 1, 2, 3, 5, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36, 48, 72, 96, 144, 312, 648, 984, 1320 and 1656 hours. | |
| Blood Volume Collected/Sample | 10 mL | |
| Blood Sample Processing/Storage | EDTA plasma samples were stored at -20°C. | |
| IRB Approval | Y | |
| Informed Consent | Y | |
| No. Enrolled | 70 | |
| No. Dosed | 70 | |
| No. Completing | 69 | |
| No. With Plasma Spls Analyzed | 70 (Incomplete samples from the dropout subject #26 were inadvertently analyzed but were not included in pharmacokinetic and statistical analyses). | |
| No. of Dropouts | 1 | |
| Length of Confinement | From 10 hours pre-dosing to 36 hours post-dosing. | |
| Restrictions | Standard dietary, activity and drug restrictions. | |
| Safety Monitoring | Vital signs (sitting blood pressure and heart rate) were assessed prior to dosing and at 12, 24, 36 and 1656 hours after dosing. Additional measurements were requested for 9 subjects and the results were clinically not significant. See page 3010 of volume 1.7 for details. | |
| Healthy Subjects Only | Y | |
| Demographics (Study #R00-724) | | |
| Age (Mean ± SD, Range) | 22.5 ± 4.6, 18-45 years | |

| | |
|---|--|
| Groups < 18 | 0 |
| 18 - 40 | 69 (98.6%) |
| 40 - 64 | 1 (1.4%) |
| 65 - 75 | 0 |
| > 75 | 0 |
| Gender | 70 Males (100%) |
| Race | 68 Caucasians (97.1%), 2 American Indians (2.9%) |
| Height (Mean \pm SD, Range) | 180.9 \pm 5.9, 170.2-195.6 cm |
| Weight (Mean \pm SD, Range) | 80.0 \pm 9.3, 59.3-102.4 Kg |

B. Study Results

1. Clinical

Dropout Information

| | |
|--------------------|---|
| Subject No | 26 |
| Reason | Subject #26 was dropped by the medical investigator after the 144 hour blood draw on day 7 due to lymphangitis which required treatment with oral antibiotic. |
| Period | N/A |
| Replacement | None |

Adverse Events Twenty one probably, seven possibly and two remotely drug related mild events, eleven occurred during treatment A and nineteen occurred during treatment B. For additional information see pages 3013-3015 of volume 1.7.

Protocol Deviations Minor deviations with respect to blood sampling times; unlikely to compromise the integrity of the study. Actual sampling times were used for all calculations.

Comments: None

2. Analytical

Comments: Analytical method is acceptable.

3. Pharmacokinetic/Statistical Analysis

Mefloquine

| | | |
|--|------------|----------------------------|
| Mean Plasma Concentrations | | Table #3, Figures #3 and 4 |
| Mean Pharmacokinetic Parameters | | Table #6 |
| Geometric Mean Ratio | | lnAUCt 0.99 |
| | | lnAUCi 0.98 |
| | | lnCmax 1.07 |
| | | Details in Table #7 |
| AUCt/AUCi ratio | Test (Fed) | Reference (Fed) |
| Mean | 0.94 | 0.93 |
| %CV | 3.41 | 4.51 |
| Range | | |

Comments: (on pharmacokinetic analysis)

- 1) For mefloquine, the Kel and AUCi values could not be determined for subject #20 during treatment B (reference).
- 2) In the pharmacokinetic analysis of mefloquine, subjects with
 - a) measurable drug concentrations at 0 hour: None
 - b) first scheduled post-dose sampling time as Tmax: None
 - c) first measurable concentration as Cmax: None
- 3) The pharmacokinetic parameters for mefloquine calculated by the reviewer are in good agreement with those determined by the firm.
- 4) The ratios of ln-transformed geometric means (Test fed/Reference fed) of AUCt, AUCi and Cmax (calculated by the reviewer and the firm) are within the acceptable limits of 0.8-1.25.

Conclusion: The single-dose parallel design post-prandial bioequivalence study is acceptable.

V. Formulation(s)

Formulation information is provided in Table #1.

Comments: The formulation for the 250 mg strength of Geneva PTC's Mefloquine Hydrochloride Tablets is acceptable.

V. Dissolution

A. Dissolution Method

There is no USP method for the dissolution testing of Mefloquine Hydrochloride Tablets. The firm has conducted dissolution testing on Mefloquine Hydrochloride Tablets, 250 mg according to following methods:

Analyte: Mefloquine

Unit: 12 tablets

Assay Method:

| Conditions | Method I (FDA method)* | Method II |
|------------------|--|---------------------------|
| Medium | Simulated Gastric Fluid without enzyme | Deionized Water |
| Volume | 900 mL | 900 mL |
| USP 24 Apparatus | I (Basket) | II (Paddle) |
| Rotation | 100 rpm | 50 rpm |
| Sampling times | 15, 30, 45 and 60 minutes | 10, 20, 30 and 40 minutes |
| Specification | % (Q) in 45 minutes | % (Q) in 30 minutes |

*Included in the telephone amendment of 7/11/01.

B. Results: The dissolution data are presented in Table #8.

C. Comments:

1) The lot numbers of the test and reference products used in the dissolution testing are the same as those used in the bio-study.

2) Tables #8 indicates that dissolution profiles of the test and reference products are similar.

3) The dissolution testing of Mefloquine Hydrochloride Tablets, 250 mg was conducted as specified in the FDA-recommended method (per the DBE electronic data base).

4) The test product, Mefloquine Hydrochloride Tablets, 250 mg, Lot #D000301 meets the FDA dissolution specification of NLT (Q) % in 45 minutes.

Recommendations

1) The single dose parallel design fasting bioequivalence study, protocol #B-12099, and the single dose parallel design fed bioequivalence study #R00-724 conducted by Geneva PTC on its Mefloquine Hydrochloride Tablets, 250 mg, Lot #D000301, comparing them to Lariam® Tablets, 250 mg, Lot #0171, manufactured by Roche Laboratories have been found acceptable by the Division of Bioequivalence. These studies demonstrate that Mefloquine Hydrochloride Tablets, 250 mg, manufactured by Geneva PTC are bioequivalent to Lariam® Tablets, 250 mg, manufactured by Roche Laboratories.

2) The in vitro dissolution testing conducted by Geneva PTC on its Mefloquine Hydrochloride Tablets, 250 mg, Lot # D000301 is acceptable.

3) The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. Dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme at 37°C using USP 24 apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

NLT (Q) % in 45 minutes.

The firm should be informed of the above recommendations.

Mamata S. Gokhale, Ph.D.
Division of Bioequivalence

JS

7/20/01

for RD INITIALED BDAVIT
FT INITIALED BDAVIT

JS

Date 7/20/01

Concur:

JS

Date 7/31/2001

f Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-175 (original, duplicate), Davit, HFD-658, Gokhale, HFD-658, Drug File, Division File

Table #1
Formulation of Mefloquine Hydrochloride Tablets, 250 mg by Geneva PTC.

| ¹ Ingredient | mg/tablet | % |
|--|-----------|--------|
| ✓ ² Mefloquine Hydrochloride | ✓250.00 | |
| ✓Microcrystalline Cellulose, NF | | |
| ✓ ³ Lactose Monohydrate, NF | | |
| ✓Pregelatinized Starch, NF | | |
| ✓Low substituted Hydroxypropyl Cellulose, NF | | |
| Purified Water, USP | | |
| ✓ Crospovidone, NF | | |
| ✓ Talc, USP | | |
| ✓Magnesium Stearate, NF | | |
| Total weight | 440.00 | 100.00 |

¹All inactive ingredients are within approved safety limits (FDA Inactive Ingredient Guide, January, 1996).

²Active Ingredient.

³Lost during processing. Used for manufacturing only. Does not appear in the final product.

**APPEARS THIS WAY
ON ORIGINAL**

Table #2
Mean Plasma Concentrations of Mefloquine
Following an Oral Dose of 3 x 250 mg (Fasting Study)
Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301
Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171

| Time (hours) | Mean (+ SD) Plasma Concentrations (ng/mL) | | | | |
|--------------|---|--------|-------------|--------|-----------|
| | Treatment A | | Treatment B | | Ratio A/B |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 1 | 57.67 | 39.74 | 63.43 | 33.94 | 0.91 |
| 5 | 639.97 | 150.33 | 717.24 | 189.94 | 0.89 |
| 10 | 656.97 | 156.26 | 730.94 | 200.53 | 0.90 |
| 15 | 622.13 | 138.15 | 724.27 | 173.26 | 0.86 |
| 20 | 552.09 | 146.61 | 615.12 | 142.56 | 0.90 |
| 22 | 521.03 | 119.99 | 583.03 | 113.06 | 0.89 |
| 24 | 567.06 | 125.91 | 612.06 | 134.46 | 0.93 |
| 26 | 609.72 | 125.91 | 662.27 | 152.88 | 0.92 |
| 28 | 643.09 | 137.80 | 696.55 | 156.75 | 0.92 |
| 30 | 608.25 | 130.21 | 656.67 | 147.40 | 0.93 |
| 32 | 599.75 | 146.20 | 636.24 | 159.28 | 0.94 |
| 34 | 616.75 | 151.54 | 658.70 | 149.03 | 0.94 |
| 36 | 616.91 | 138.84 | 647.45 | 159.42 | 0.95 |
| 38 | 614.28 | 141.16 | 648.12 | 162.73 | 0.95 |
| 40 | 579.78 | 124.11 | 614.36 | 141.51 | 0.94 |
| 44 | 504.19 | 110.87 | 536.67 | 120.31 | 0.94 |
| 48 | 538.50 | 120.39 | 551.15 | 108.39 | 0.98 |
| 72 | 523.00 | 115.51 | 557.06 | 137.50 | 0.94 |
| 120 | 511.38 | 148.99 | 504.12 | 125.20 | 1.01 |
| 168 | 442.29 | 108.42 | 469.97 | 138.47 | 0.94 |
| 336 | 303.28 | 76.01 | 334.85 | 120.59 | 0.91 |
| 672 | 173.94 | 60.23 | 176.85 | 85.70 | 0.98 |
| 1008 | 98.95 | 41.08 | 99.25 | 53.93 | 1.00 |
| 1344 | 64.13 | 30.52 | 63.73 | 37.00 | 1.01 |
| 1680 | 43.35 | 23.86 | 45.11 | 33.49 | 0.96 |
| 2016 | 27.75 | 18.74 | 29.32 | 23.22 | 0.95 |
| 2688 | 13.26 | 13.96 | 11.15 | 12.83 | 1.19 |

Table #3
Mean Plasma Concentrations of Mefloquine
Following an Oral Dose of 3 x 250 mg (Fed Study)
Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301
Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171

| Time (hours) | Mean (\pm SD) Plasma Concentrations (ng/mL) | | | | |
|--------------|--|--------|-------------|--------|-----------|
| | Treatment A | | Treatment B | | Ratio B/A |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 1 | 208.32 | 163.94 | 100.01 | 97.93 | 2.08 |
| 2 | 635.96 | 335.52 | 429.31 | 237.13 | 1.48 |
| 3 | 847.68 | 329.96 | 743.34 | 326.98 | 1.14 |
| 5 | 1035.26 | 359.84 | 946.80 | 364.94 | 1.09 |
| 8 | 1022.53 | 336.74 | 961.77 | 471.50 | 1.06 |
| 10 | 943.56 | 303.36 | 878.14 | 346.18 | 1.07 |
| 12 | 905.97 | 362.40 | 877.00 | 359.63 | 1.03 |
| 14 | 855.26 | 236.19 | 849.51 | 340.13 | 1.01 |
| 16 | 878.24 | 235.74 | 865.57 | 323.74 | 1.01 |
| 18 | 841.21 | 326.90 | 767.20 | 338.42 | 1.10 |
| 20 | 807.76 | 339.60 | 750.31 | 316.26 | 1.08 |
| 22 | 774.76 | 266.36 | 724.86 | 325.04 | 1.07 |
| 24 | 821.15 | 286.19 | 749.54 | 371.87 | 1.10 |
| 26 | 873.41 | 318.85 | 789.89 | 370.24 | 1.11 |
| 28 | 823.94 | 254.50 | 827.03 | 411.58 | 1.00 |
| 30 | 849.32 | 231.21 | 769.80 | 275.02 | 1.10 |
| 32 | 857.85 | 207.31 | 809.37 | 289.00 | 1.06 |
| 36 | 789.68 | 229.07 | 753.40 | 298.45 | 1.05 |
| 48 | 759.41 | 230.27 | 761.63 | 265.51 | 1.00 |
| 72 | 755.65 | 273.52 | 715.63 | 223.99 | 1.06 |
| 96 | 671.38 | 211.98 | 625.91 | 226.31 | 1.07 |
| 144 | 560.41 | 181.14 | 581.91 | 235.41 | 0.96 |
| 312 | 444.44 | 192.69 | 447.85 | 172.72 | 0.99 |
| 648 | 248.08 | 107.57 | 266.35 | 108.94 | 0.93 |
| 984 | 128.29 | 60.48 | 144.04 | 82.67 | 0.89 |
| 1320 | 85.03 | 48.79 | 92.93 | 53.57 | 0.91 |
| 1656 | 51.79 | 35.92 | 54.80 | 39.66 | 0.95 |

Table #4
Mefloquine Pharmacokinetic Parameters
Single-Dose Fasting Study, 3x250 mg Dose
Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301
Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171

| Plasma Parameters | Cmax (ng/mL) | | Tmax (hours) | | Kel (1/hours) | |
|-------------------|--------------|--------|--------------|--------|---------------|-------|
| | A | B | A | B | A | B |
| MEAN | 723.28 | 783.85 | 20.75 | 23.06 | 0.001 | 0.001 |
| CV% | 21.03 | 26.43 | 106.67 | 246.68 | 31.64 | 38.85 |

| Plasma Parameters | T1/2 (hours) | | AUCt (ng/mL-hours) | | AUCi (ng/mL-hours) | |
|-------------------|--------------|--------|--------------------|-----------|--------------------|-----------|
| | A | B | A | B | A | B |
| MEAN | 573.07 | 577.35 | 346266.75 | 360308.61 | 364108.69 | 377430.76 |
| CV% | 26.22 | 34.90 | 29.19 | 38.28 | 30.26 | 38.12 |

Table #5
Summary Statistics for Mefloquine
Single-Dose Fasting Study, 3x250 mg Dose
Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301
Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171

| PK Parameter (Treatment) | Geometric Mean | | Ratio B/A | 90% C.I. |
|--------------------------|----------------|-----------|-----------|--------------|
| | A | B | | |
| lnAUCt (ng·hr/mL) | 332378.61 | 338706.19 | 0.98 | 85.89-112.10 |
| lnAUCi (ng·hr/mL) | 348631.44 | 355003.42 | 0.98 | 85.86-112.32 |
| lnCmax (ng·hr/mL) | 707.82 | 758.42 | 0.93 | 84.55-103.01 |

Table #6**Mefloquine Pharmacokinetic Parameters****Single-Dose Fed Study, 3x250 mg Dose****Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301****Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171**

| Plasma Parameters | Cmax (ng/mL) | | Tmax (hours) | | Kel (1/hours) | |
|-------------------|--------------|---------|--------------|--------|---------------|-------|
| | A | B | A | B | A | B |
| MEAN | 1211.09 | 1152.29 | 23.03 | 23.00 | 0.002 | 0.002 |
| CV% | 28.55 | 35.38 | 232.49 | 229.21 | 16.44 | 22.68 |

| Plasma Parameters | T1/2 (hours) | | AUCt (ng/mL-hours) | | AUCi (ng/mL-hours) | |
|-------------------|--------------|--------|--------------------|-----------|--------------------|-----------|
| | A | B | A | B | A | B |
| MEAN | 409.82 | 429.94 | 429469.65 | 437459.69 | 463116.59 | 475733.94 |
| CV% | 17.33 | 24.36 | 35.07 | 36.59 | 38.26 | 39.69 |

Table #7**Summary Statistics for Mefloquine****Single-Dose Fed Study, 3x250 mg Dose****Treatment A (Test): Mefloquine HCl Tablets, 250 mg, Lot #D000301****Treatment B (Reference): Lariam® Tablets, 250 mg, Lot #0171**

| PK Parameter (Treatment) | Geometric Mean | | Ratio A/B |
|--------------------------|----------------|-----------|-----------|
| | A | B | |
| lnAUCt (ng·hr/mL) | 404374.62 | 410408.06 | 0.99 |
| lnAUCi (ng·hr/mL) | 432135.77 | 442477.68 | 0.98 |
| lnCmax (ng·hr/mL) | 1167.97 | 1090.02 | 1.07 |

Table #8
Results of In Vitro Dissolution Testing
Test Product: Mefloquine Tablets, 250 mg by Geneva PTC
Reference Product: Lariam® Tablets, 250 mg by Roche Laboratories

| Medium: 900 mL Deionised Water, Apparatus: Paddle, Speed: 50 rpm, n=12 | | | | | | |
|---|----------------------------------|--------------|-------------|------------------------------------|--------------|-------------|
| Sampling Times (min.) | Test Product Lot #D000301 | | | Reference Product Lot #0171 | | |
| | Mean % | Range | % CV | Mean % | Range | % CV |
| 10 | 79.3 | | 1.7 | 80.9 | | 12.5 |
| 20 | 86.2 | | 2.7 | 88.5 | | 5.5 |
| 30 | 88.0 | | 3.3 | 90.2 | | 1.8 |
| 40 | 88.4 | | 2.9 | 90.7 | | 1.3 |

| Medium: 900 mL SGF w/o enzyme, Apparatus: Basket, Speed: 100 rpm, n=12 | | | | | | |
|---|----------------------------------|--------------|-------------|------------------------------------|--------------|-------------|
| Sampling Times (min.) | Test Product Lot #D000301 | | | Reference Product Lot #0171 | | |
| | Mean % | Range | % CV | Mean % | Range | % CV |
| 15 | 59.0 | | 4.3 | 63.8 | | 8.7 |
| 30 | 74.0 | | 3.5 | 82.7 | | 4.0 |
| 45 | 81.5 | | 3.3 | 88.4 | | 3.7 |
| 60 | 84.5 | | 3.4 | 91.7 | | 3.5 |

Figure 1

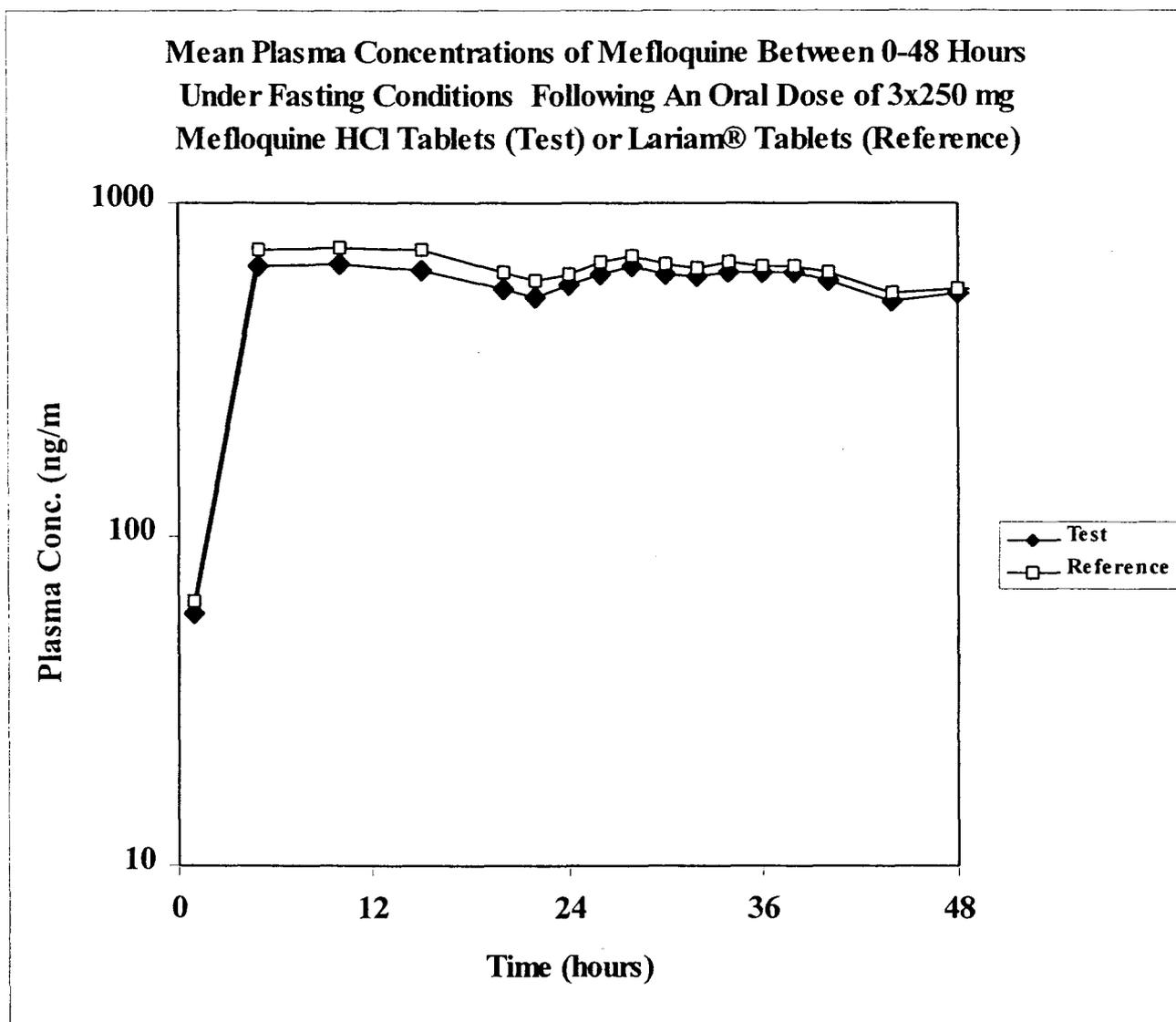


Figure 2

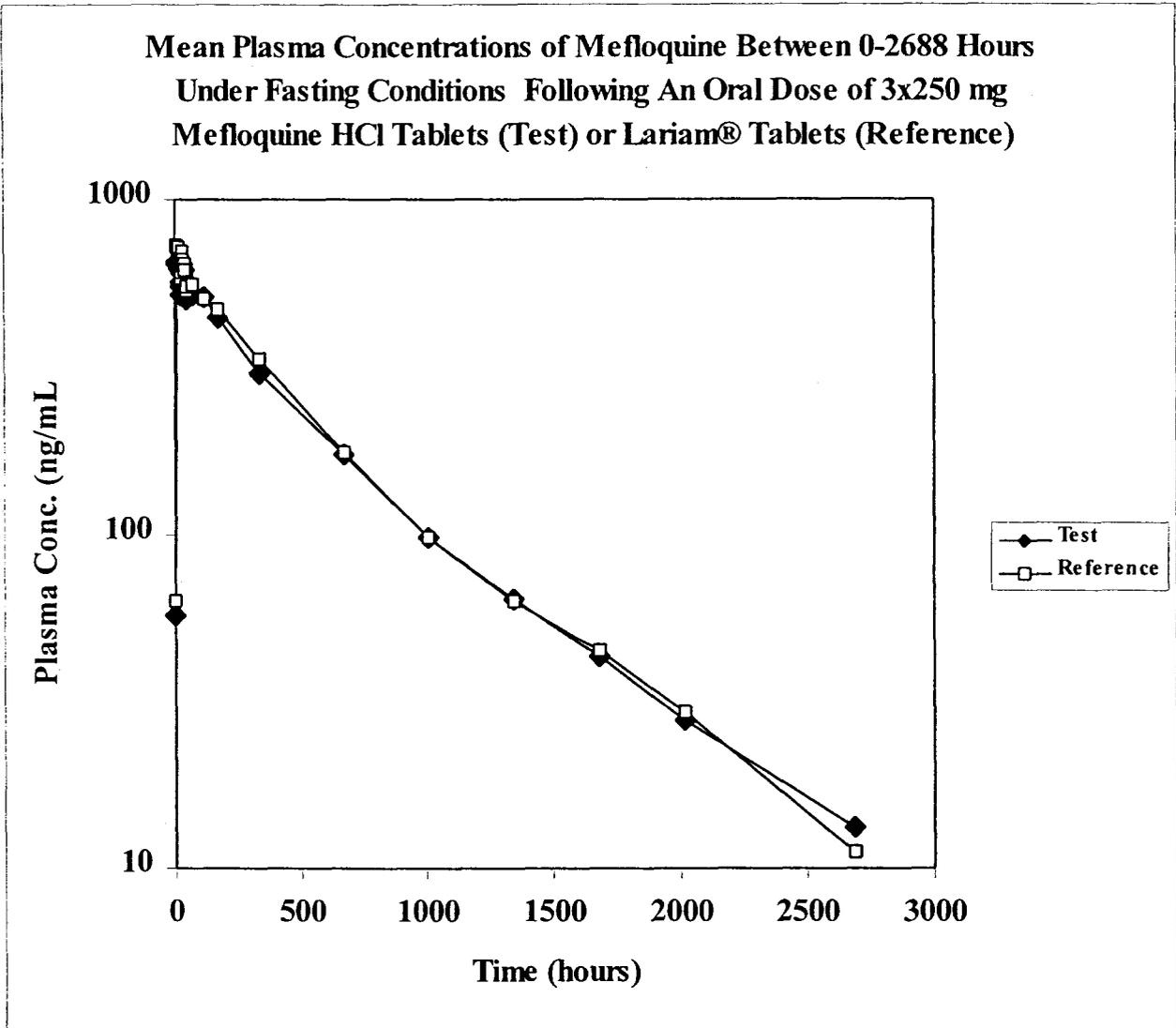


Figure 3

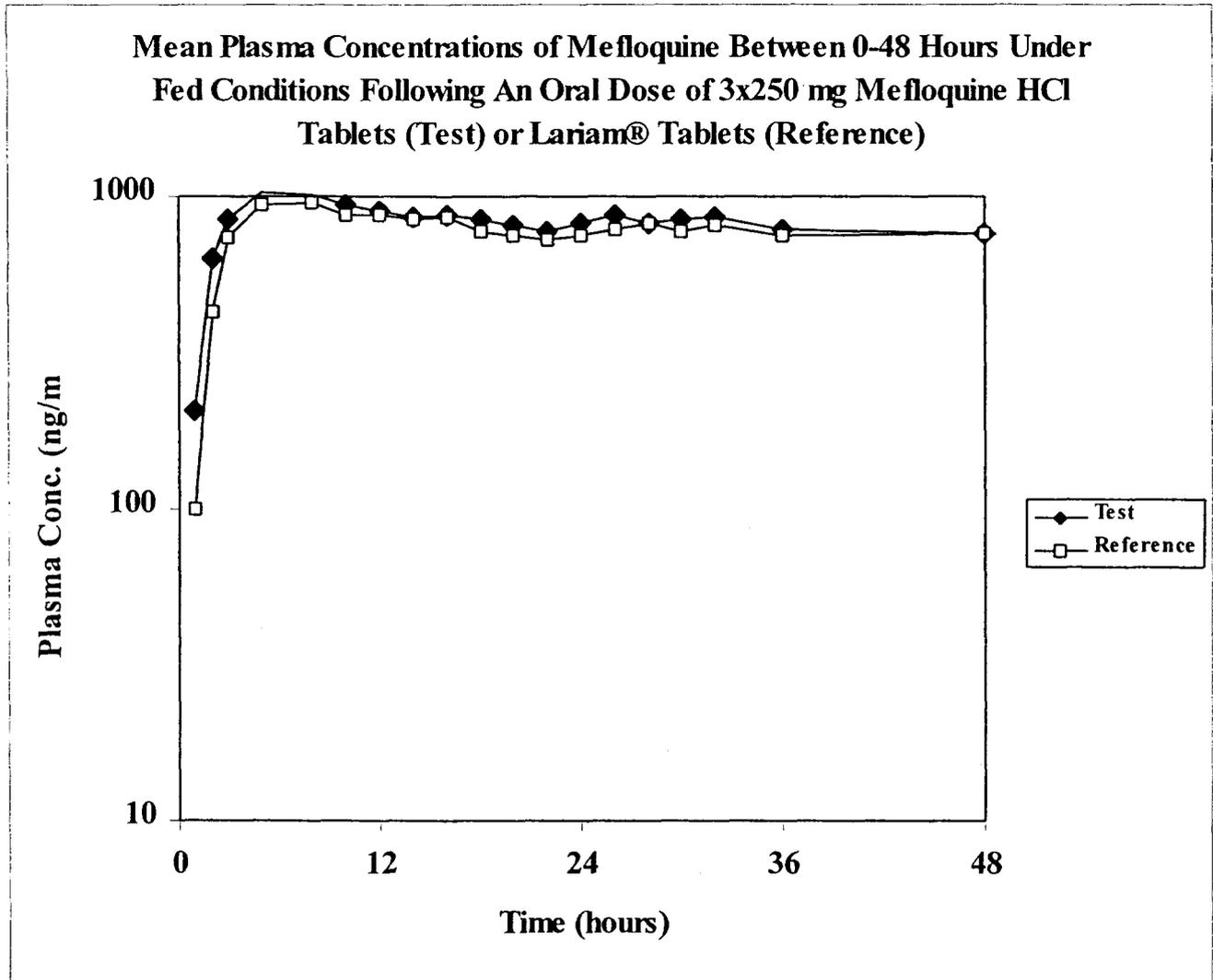


Figure 4

