CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-232

BIOEQUIVALENCE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #75-232 SPONSOR: L. Perrigo Company
DRUG: Loperamide Hydrochloride Tablet (small caplet)
DOSAGE FORM: small caplet
STRENGTHS/(s): 2 mg
TYPE OF STUDY: Single Dose, Fasting
STUDY SITE: Phoenix International

STUDY SUMMARY: The 90% confidence intervals for loperamide and desmethylloperamide log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits. The fasting study is acceptable.

DISSOLUTION: The dissolution testing was done by USP method: 900 mL of 0.1N HCl using apparatus 2 (paddles) at 50 rpm. The test product dissolves more than n 30 minutes and meets USP specifications.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: KRDhariwal DATE 9/29/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: [signature] DATE 10/1/1998

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: [signature] DATE 10/27/98

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

Loperamide Hydrochloride Tablets
Small Caplet Dosage Form, 2 mg
ANDA #75-232
Reviewer: Kuldeep R. Dhariwal
File name: 75232SD.798

L. Perrigo Company
117 Water Street
Allegan, MI 49010
Submission Date:
July 9, 1998

Response to Review of Bioequivalence Study and Dissolution Data

The firm submitted fasting bioequivalence study and dissolution data comparing its loperamide hydrochloride tablets (small caplet form), 2 mg with McNeil's Imodium® A-D caplets, 2 mg on February 23, 1998. The study was found incomplete and the deficiency comments were sent to the firm (file name: 75232SD.298). The firm has submitted the response to the deficiency comments in this amendment.

1. Deficiency #1: You have stated that the original validated method was modified for mode of detection, reconstitution volume, and concentration of internal standard. Since the method was modified, you reassessed within and between batch precision and accuracy, internal standard recovery, specificity and sensitivity of the assay. The submitted supporting data are from the curves GYX33, GYX34, GYX42, GYX50, and GYX57. However, three curves (GYX42, GYX50, and GYX57) are from study sample analyses and are not separate method validation curves. Please Comment.

Response: ..... (Analytical Method Validation), Section 8, states '... Analytical method parameters which are suitable at the time of validation may not be the best choice at the time of a study due to changes in equipment, environmental conditions, detector conditions, detector characteristics, etc. Hence, at times it is necessary to change a method after validation. Generally, partial revalidation is required for such changes and data generated during analysis of study samples are usually adequate for this purpose... All data which substantiate the change must be incorporated into a revised validation report'.

Partial revalidation of loperamide was required due to assay changes (i.e modified mode of detection, reconstitution volume, and concentration of internal standard (IS)); the latter changes to the validation were necessary due to an inability to derive acceptable assay specificity prior to study sample analysis. As a result of the assay changes, partial revalidation was to be performed, including the reassessment of within and between batch precision and accuracy, sensitivity, specificity, and due to change in the IS working solution concentration, IS recovery. As per within and between batch precision and accuracy was assessed as part of analytical batches GYX33, GYX34, GYX42, GYX50, and GYX57, in which subject samples may or may not have been extracted, i.e. following the successful extraction of two analytical batches (GYX33, GYX34) in which no study samples were extracted, study sample analysis commenced; sensitivity and between batch precision and accuracy data was derived utilizing data generated as part of GYX33, GYX34, and three subsequent analytical batches in which study samples were assayed (GYX42, GYX50, and GYX57).

Reviewer's Comment: Response is satisfactory.

2. Deficiency #2: When was the analytical method modified? Before this study or during the study? Were all the study samples assayed using the modified method? If the method was modified before this study, why was it not revalidated before analyzing the study samples?

Response: During the 'lead-in' portion of this study, difficulties in deriving assay specificity using the extraction and instrumentation procedures detailed in the SOP utilized during method validation, produced the need for a change in the mode of detection. Thus, specificity was re-evaluated using Acceptable results were observed (i.e. specificity was obtained) and re-validation commenced. Method used during validation, was modified to method (authorized August 14, 1997) to incorporate the change in detection mode prior to study sample analysis (August 20, 1997). Changes to the reconstitution volume and IS concentration used during study sample extraction were incorporated in the method SOP several days following commencement of sample analysis (method SOP authorized September 2, 1997); however, all study samples were analyzed according to the conditions specified in

the revised or method with SOP deviations). The partial validation was performed according SOP using additional data generated during study sample analysis.

Reviewer's comment: Response is satisfactory.

3. Deficiency #3: Please submit the validation results of original method.

Response: The previous version of the method validation report is enclosed in the amendment.

4. Deficiency #4: Please state the differences in the mode of detection, reconstitution volume, and concentration of internal standard used in original and modified method. Also, submit

Response: The original detection mode, (or single ion monitoring was modified to a method (multiple reaction monitoring, ; the latter is a more specific mode of detection. The reconstitution volume was changed from µL to minimize the observed variability of analyte and IS responses, and the internal standard working solution concentration was modified form to optimize response. Both method SOP versions are enclosed in the amendment.

Reviewer's comment: Response is satisfactory.

5. Deficiency #5: Dissolution: Please provide %CV at each sampling time.

Response: The %CV at each sampling time are provided.

Reviewer's comment: Response is satisfactory.

Comments:

1. The firm has satisfactorily responded to all deficiencies. The fasting bioequivalence study is acceptable.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Perrigo Company on its loperamide hydrochloride tablets (small caplet), 2 mg, lot #7P0510 comparing it to Imodium® A-D tablet (caplet), 2 mg, lot #SPA648 manufactured by McNeil has been found acceptable to the Division of Bioequivalence. The study demonstartes that under fasting conditions, Perrigo's loperamide hydrochloride tablets (small caplet) 2 mg is bioequivalent to the reference product Imodium® A-D tablet (caplet) 2 mg manufactured by McNeil.

2. The dissolution testing conducted by the firm on its test product is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddles) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of the dosage form is dissolved in 30 minutes.

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

Dhariwal.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 10/1/1998

Concur: _____ Date 10/27/98
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Loperamide Hydrochloride Tablets (small caplets)
Dose Strength: 2 mg
ANDA No.: 75-232
Firm: Perrigo
Submission Date: July 9, 1998
File Name: 75232SD.798

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 mL
Specifications: NLT in 30 minutes
Reference Drug: Imodium® A-D (McNeil)
Assay Methodology

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #7P0510 Strength(mg) 2			Reference Product Lot #SPA648 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	92		3.5	59		14.0
30	97		2.5	80		8.8
45	97		2.7	88		6.4
60	98	94	2.2	92		4.6

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

JUN 2 1998

Loperamide Hydrochloride Tablets
Small Caplet Dosage Form, 2 mg
ANDA #75-232
Reviewer: Kuldeep R. Dhariwal
File name: 75232SD.298

L. Perrigo Company
117 Water Street
Allegan, MI 49010
Submission Date:
February 23, 1998

Review of Bioequivalence Study and Dissolution Data

The firm has submitted fasting bioequivalence study and dissolution data comparing its loperamide hydrochloride tablets (small caplet form), 2 mg with McNeil's Imodium® A-D caplets, 2 mg. L. Perrigo has an approved ANDA 74-194 for loperamide HCl, 2 mg caplets. This new submission is in response to a formulation change by the reference listed drug to a small caplet form. Since the firm reformulated its product, it is submitted with separate bioequivalence study under new ANDA.

Introduction:

Loperamide HCl prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Clinical studies have indicated that apparent elimination half-life of this drug is 10.8 hours (9.1-14.4 hours). Plasma levels of unchanged drug remain below 2 ng/mL after the intake of 2 mg capsule.

Janssen as the innovator markets the 2 mg capsule under the brand name Imodium® which is a prescription drug product. McNeil markets a liquid (1 mg/5 mL), 2 mg chewable tablet, and 2 mg caplet (all OTC) under the brand name Imodium® A-D.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol #: 941785
IRB approval: Yes
Consent Form Signed: Yes

Clinical Site: Phoenix International
Principal Investigator: Pierre Geoffroy, M.Sc., M.D., C.M.
Analytical Facility:
Analytical Director:
Study Dates: Period I June 30-July 7, 1997
Period II July 21-28, 1997
Analysis Dates: August 20-September 16, 1997
Storage Period: 78 days
Study Design: Randomized, two-way crossover design with a washout period of 21 days
Randomization Scheme: AB: 1,2,3,8,9,10,12,14,15,20,21,22,26, 29,30,32
BA: 4,5,6,7,11,13,16,17,18,19,23,24,25, 27,28,31

Treatments:

A: Loperamide hydrochloride caplets, 5x2 mg; Perrigo Company, Lot #7P0510; Lot size: caplets; Manufacture date: 2/1997; Assay: 99%; Content Uniformity: 98%

B: Imodium® A-D caplets, 5x2 mg; McNeil; Lot #SPA648; Expiry Date: 9/99; Assay: 100.5%; Content Uniformity: 100%

Formulation of test product: Table 1

Subjects: 30 male subjects and 2 alternate male subjects in the age range 18-45 years were enrolled in the study according to inclusion/exclusion criteria specified in the protocol. Protocol specified that samples from subjects 1-30 will be analyzed.

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

Dosing: After 10 hour fast, with 240 mL of water. Water was not allowed within one hour of dosing. No food for 4 hours post-dose.

Sample Collection: Blood samples were collected at predose (0 h) and at following time post-dose: 0.33,0.67,1,

2,3,4,5,6,7,8,9,10,12,16,24,36,48,72,96,120 and 168 hours. Plasma was separated and stored at -12°C or lower.

B. Study Results:

1. Clinical:

Drop-outs: Of the 32 subjects enrolled in the study, 31 completed the study. Subject #13 was withdrawn due to lower respiratory tract infection/viral bronchitis. As per protocol, statistical and pharmacokinetic analyses were performed on data from subjects 1-12 and 14-31.

Adverse events: Some subjects experienced headache, nausea, dizziness and cold.

Protocol Deviations: There were several sampling deviations. Actual times were used for calculations.

2. Analytical:

Method:

Internal Standard:

Linearity: Standard curve range for loperamide was 0.100 ng/mL to 2.996 ng/mL and from 0.100 ng/mL to 5.005 ng/mL for desmethylloperamide. Correlation coefficients were greater than 0.992.

Regression: 1/Concentration (Linear)

QC Samples: Loperamide:
0.300 ng/mL, 1.001 ng/mL, 2.401 ng/mL
Desmethylloperamide:
0.300 ng/mL, 2.498 ng/mL, 3.996 ng/mL

Accuracy: Loperamide:
Standards: 97.9% to 103.6%
QC samples: 100.3% to 101.0%
Desmethylloperamide:
Standards: 97.9% to 103.1%
QC samples: 99.9% to 100.2%

Precision:

Loperamide:
- Standards: 3.9% to 6.6%
- QC samples: 5.2% to 6.6%

Desmethylloperamide:
- Standards: 3.8% to 7.6%
- QC samples: 5.4% to 7.8%

Reassays:

Loperamide:
19 due to poor chromatography
10 due to above upper limit of std. curve
5 due to lost in processing
1 due to anomalous sample value

Desmethylloperamide:
24 due to poor chromatography
69 due to above upper limit of std. curve
6 due to lost in processing
2 due to anomalous sample value
1 H/L std. missing from the regression

The firm has provided following pre-study method validation results:

Recovery:

Loperamide	
0.300 ng/mL	64.48% (9.0% CV)
1.000 ng/mL	70.81% (9.0% CV)
2.399 ng/mL	68.78% (10.7% CV)
Desmethylloperamide	
0.300 ng/mL	75.25% (16.7% CV)
2.498 ng/mL	77.76% (8.3% CV)
3.996 ng/mL	72.73% (9.7% CV)
Astemizole (Internal Standard)	
320.4 ng/mL	84.49% (5.6% CV)

Stability:

a) Bench-top: Loperamide and desmethylloperamide are stable in plasma left at room temperature for 6 hours before extraction.

b) Stability-after extraction: Loperamide and desmethylloperamide are stable in samples stored at room temperature for 22 hours after extraction and reconstitution.

c) Freeze-thaw: Stable over 6 cycles.

d) Long-term stability: Stability demonstrated for 154 days. Study samples were stored for no more than 78 days.

The submitted validation data for stability and recovery of the analytes and internal standard are from the experiments carried out before conducting this study. The firm states that the original validated method was modified for mode of detection, reconstitution volume, and concentration of internal standard. Since the method was modified, the firm reassessed within and between batch precision and accuracy, internal standard recovery, specificity and sensitivity of the assay. The submitted supporting data are from the curves GYX33, GYX34, GYX42, GYX50, and GYX57. However, three curves (GYX42, GYX50, and GYX57) are from study sample analyses and are not separate method validation curves.

3. Pharmacokinetics/Statistics:

Loperamide:

Mean plasma concentrations:	Table 2 and Figure 1	
Pharmacokinetic parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	91.56-110.16%
	$LAUC_{0-inf}$	91.63-109.12%
	LC_{max}	93.15-113.83%

The test/reference ratios for AUC_{0-t} ranged from 0.60-2.03 (mean 1.05), AUC_{0-inf} ranged from 0.66-2.04 (mean 1.04), and for C_{max} ranged from 0.63 to 1.87 with a mean of 1.08.

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.76 to 0.95 for test and from 0.80 to 0.96 for reference product.

Desmethylloperamide:

Mean plasma concentrations:	Table 3 and Figure 2	
Pharmacokinetic parameters:	Table 3	
90% Confidence Intervals:	$LAUC_{0-t}$	92.84-100.06%
	$LAUC_{0-inf}$	93.00-100.33%
	LC_{max}	93.39-101.10%

The test/reference ratios for AUC_{0-t} ranged from 0.78-1.28 (mean 0.97), AUC_{0-inf} ranged from 0.80-1.27 (mean 0.97), and for C_{max} ranged from 0.79 to 1.35 with a mean of 0.98.

The AUC_{0-t}/AUC_{0-inf} ratios ranged from 0.88 to 0.98 for test and from 0.89 to 0.97 for reference product.

Comments:

1. The pharmacokinetic parameters and 90% confidence intervals were recalculated by the reviewer. The reported values are in good agreement with those obtained by the reviewer.

2. The elimination constant and therefore AUC_{0-inf} could not be calculated for loperamide for subject #29 on test and reference products.

3. The 90% confidence intervals for log transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are within acceptable limits of 80-125%. A statistically significant sequence effect for loperamide was observed for all the three parameters. The study meets the criteria for acceptability of studies with sequence effects listed in the Division guidance on statistical procedures: it is a single dose study using a standard two-treatment crossover design in normal healthy volunteers, the drug is not an endogenous entity, the study was based on a acceptable protocol and used a validated assay methodology etc.

4. The fasting study is incomplete because of the deficiencies in analytical methods (see deficiencies).

5. In this study, subjects were dosed with 5x2 mg tablets (small caplets). The dosing instructions for innovator are: take 2 caplets after the first loose bowel movement and 1 caplet after each subsequent loose bowel movement but no more than 4 caplets a day for no more than 2 days. The firm has therefore exceeded the maximum daily dose. The bio-study for Perrigo's approved ANDA (#74194) was done using 5x2 mg tablets. This drug is an OTC product.

In Vitro Dissolution Testing:

The firm has submitted dissolution testing results on test and reference products. The firm has conducted dissolution tests using USP method: apparatus 2 (paddles) at 50 rpm in 900 mL of o.1N HCl. The firm has also conducted dissolution tests in 500 mL of acetate buffer, pH 4.7 using apparatus 2 at 50 rpm. The USP

method will be recommended for stability and quality control programs.

The test product meets the specifications. Six of the twelve reference tablets dissolve less than in 30 minutes and do not meet the specifications. However, both test and reference products meet the specifications in acetate buffer.

Deficiencies:

1. It is not clear when the analytical method was modified? Before this study or during the study? Were all the study samples assayed using the modified method? If the method was modified before this study, why was it not revalidated before analyzing the study samples?

2. The firm needs to submit the validation results of original method.

3. The firm should state the differences in the mode of detection, reconstitution volume, and concentration of internal standard used in original and modified method. The firm should submit

4. Dissolution: The firm should provide %CV at each sampling time.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Perrigo Company on its loperamide hydrochloride tablets (small caplet), 2 mg, lot #7P0510 comparing it to Imodium® A-D tablet (caplet), 2 mg, lot #SPA648 manufactured by McNeil has been found incomplete by the Division of Bioequivalence.

2. The dissolution testing conducted by the firm on its test product is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.1N HCl using apparatus 2 (paddles) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the dosage form is dissolved in 30 minutes.

3. From bioequivalence point of view, the firm has met the requirements of *in vitro* dissolution testing but not of *in vivo* bioequivalency and the application is incomplete.

6/1/93

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR Date 6/2/1998

Concur: Date 6/2/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

TABLE 2
MEAN PLASMA LOPERAMIDE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS (n=30)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	0.23	0.25	0.22	0.22	1.07
0.67	0.75	0.37	0.66	0.38	1.15
1	1.01	0.51	0.85	0.47	1.18
2	1.36	0.69	1.24	0.67	1.09
3	1.52	0.68	1.36	0.64	1.12
4	1.55	0.70	1.49	0.63	1.04
5	1.65	0.69	1.63	0.64	1.01
6	1.56	0.66	1.59	0.63	0.98
7	1.42	0.59	1.43	0.55	0.99
8	1.29	0.51	1.34	0.53	0.96
9	1.15	0.46	1.19	0.48	0.97
10	1.08	0.46	1.10	0.48	0.98
12	0.86	0.36	0.87	0.36	1.00
16	0.63	0.28	0.63	0.30	1.00
24	0.46	0.20	0.47	0.19	0.98
36	0.27	0.13	0.27	0.13	0.99
48	0.16	0.10	0.16	0.11	1.00
72	0.03	0.06	0.02	0.05	1.20
96	0.00	0.02	0.00	0.00	.
120	0.00	0.00	0.00	0.00	.
168	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI*	34.77	14.16	34.37	14.04	1.01
AUCT	30.12	13.91	29.71	13.76	1.01
CMAX	1.81	0.76	1.73	0.66	1.05
KE*	0.04	0.01	0.04	0.01	1.00
LAUCI	32.03	0.42	31.96	0.38	1.00
LAUCT	27.01	0.49	26.89	0.46	1.00
LCMAX	1.66	0.43	1.61	0.38	1.03
THALF	17.13	3.59	16.78	2.54	1.02
TMAX	4.40	1.45	5.00	1.46	0.88

*n=29

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	34.57	34.26	1.01	92.02	109.81
AUCT	30.12	29.71	1.01	91.92	110.85
CMAX	1.81	1.73	1.05	94.21	115.18
LAUCI	31.85	31.85	1.00	91.63	109.12
LAUCT	27.01	26.89	1.00	91.56	110.16
LCMAX	1.66	1.61	1.03	93.15	113.83

TABLE 3
MEAN PLASMA DESMETHYLLOPERAMIDE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=30

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	0.02	0.05	0.02	0.07	1.01
0.67	0.36	0.26	0.30	0.24	1.19
1	0.81	0.45	0.67	0.43	1.21
2	1.90	0.85	1.68	0.91	1.13
3	2.56	0.94	2.36	1.02	1.08
4	3.03	1.20	2.97	0.99	1.05
5	3.96	0.96	3.93	0.98	1.01
6	4.17	1.07	4.19	0.90	0.99
7	4.06	0.92	4.22	0.89	0.96
8	4.08	0.88	4.25	0.92	0.96
9	3.88	0.83	4.07	0.83	0.95
10	3.94	0.87	4.06	0.81	0.97
12	3.51	0.66	3.56	0.69	0.98
16	2.98	0.72	3.02	0.71	0.99
24	2.47	0.56	2.54	0.54	0.97
36	2.08	0.52	2.13	0.40	0.98
48	1.56	0.43	1.61	0.40	0.97
72	0.97	0.29	1.00	0.29	0.98
96	0.60	0.24	0.61	0.22	0.98
120	0.38	0.17	0.42	0.17	0.90
168	0.15	0.11	0.17	0.10	0.85

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

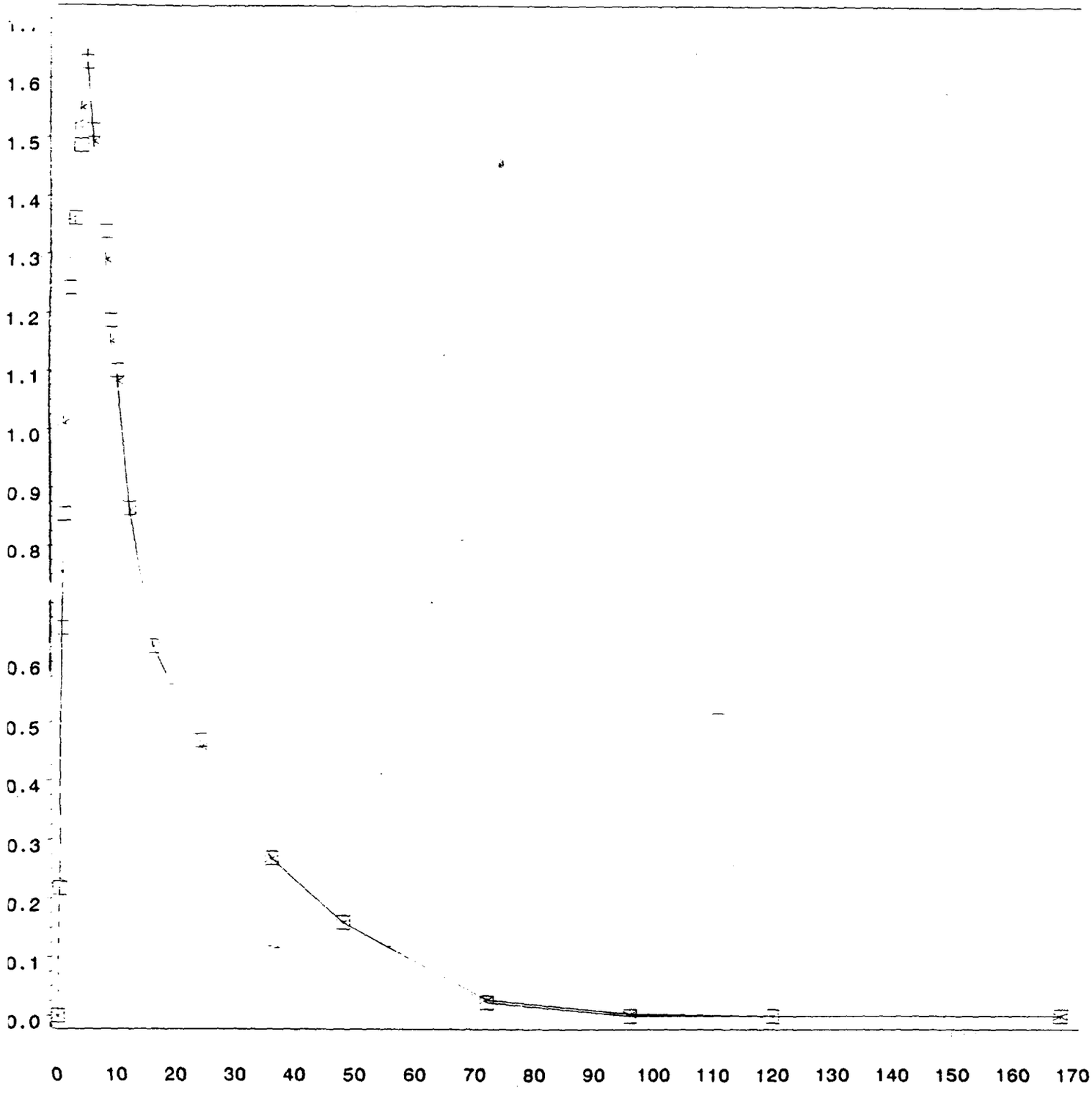
	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	204.53	50.84	210.57	47.97	0.97
AUCT	194.10	48.25	200.07	44.48	0.97
CMAX	4.50	1.04	4.59	0.88	0.98
KE	0.02	0.00	0.02	0.00	1.04
LAUCI	198.20	0.26	205.19	0.23	0.97
LAUCT	188.11	0.26	195.17	0.23	0.96
LCMAX	4.39	0.22	4.51	0.18	0.97
THALF	35.30	7.11	36.49	6.60	0.97
TMAX	7.27	1.89	7.64	2.30	0.95

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	204.53	210.57	0.97	93.33	100.94
AUCT	194.10	200.07	0.97	93.29	100.74
CMAX	4.50	4.59	0.98	93.73	102.17
LAUCI	198.20	205.19	0.97	93.00	100.33
LAUCT	188.11	195.17	0.96	92.84	100.06
LCMAX	4.39	4.51	0.97	93.39	101.10

FIG 1. PLASMA LOPERAMIDE LEVELS

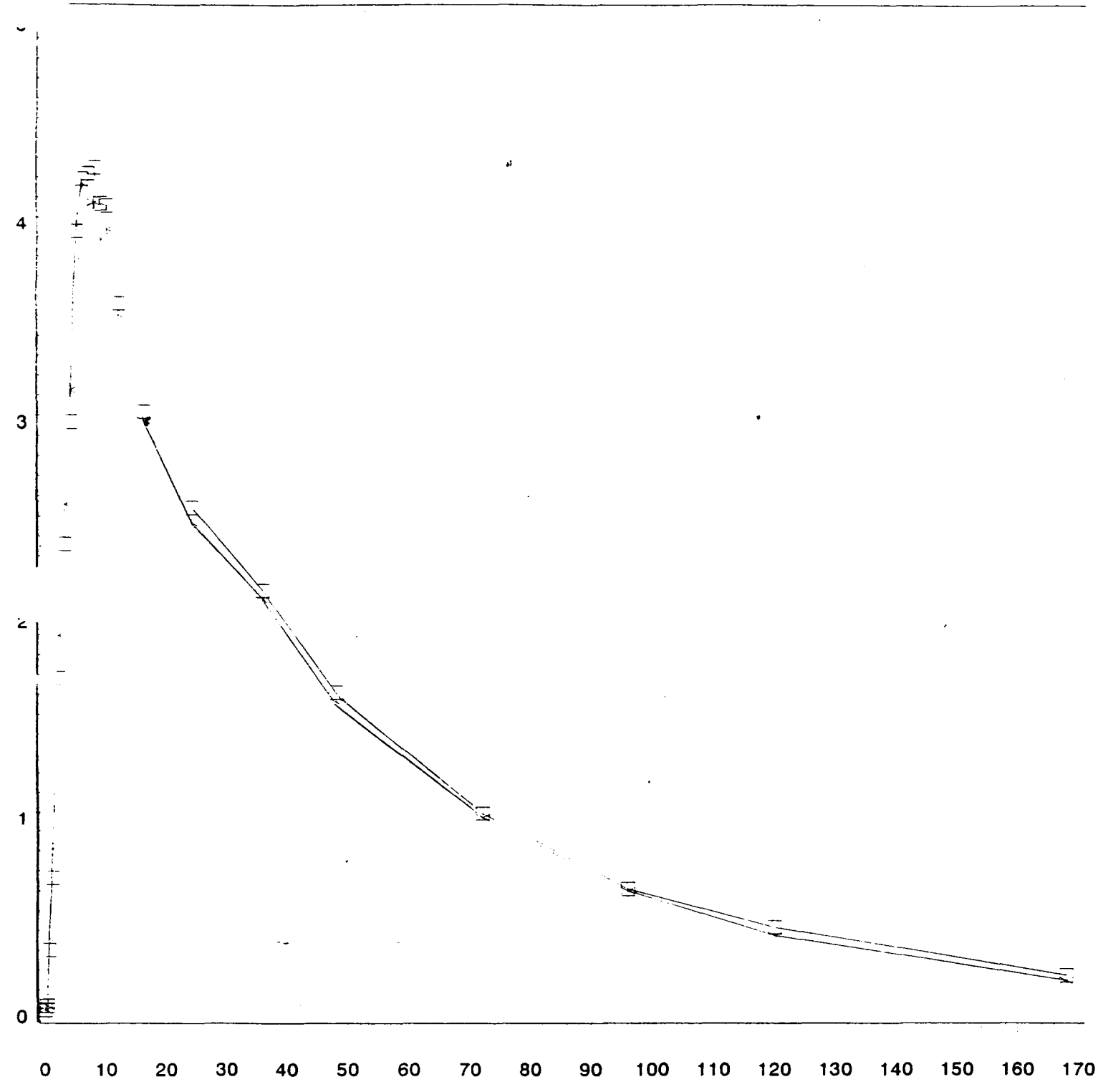
LOPERAMIDE HYDROCHLORIDE TABLETS, 2 MG, ANDA #75-232
UNDER FASTING CONDITIONS
DOSE=5 X 2 MG



1=TEST(PERRIGO) 2=REF(McNEIL)

IG 2. PLASMA DESMETHYLLOPERAMIDE LEVELS

LOPERAMIDE HYDROCHLORIDE TABLETS, 2 MG, ANDA #75-232
UNDER FASTING CONDITIONS
DOSE=5 X 2 MG



1=TEST(PERRIGO) 2=REF(McNEIL)