CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40249

BIOEQUIVALENCY REVIEW(S)

2.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-249 APPLICANT: Kiel Laboratories

DRUG PRODUCT: Orphenadrine Citrate ER Tablets, 100 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37° C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following interim specifications:
>
> 1 hour: %
> 4 hours: %
> 12 hours: NLT %

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,

/S/

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

Orphenadrine Citrate
Extended Release Tablets, 100 mg
ANDA #40-249
Reviewer: Kuldeep R. Dhariwal
File name: 40249SD.398

Kiel Laboratories, Inc.
2225, Centennial Drive
Gainesville
Georgia 30504
Submission Date:
March 26, 1998

Response to Review of Bioequivalence Studies and Dissolution Data

Background:

Kiel Laboratories previously submitted single-dose *in vivo* bioequivalence studies under fasting and non-fasting conditions and dissolution data comparing its orphenadrine citrate extended release tablets, 100 mg with Norflex® tablets (3M Pharmaceuticals). The studies were found incomplete and the comments were sent to the firm. The firm submitted the response as amendment on March 26, 1998 which was assigned to this reviewer on July 20, 1998.

Response:

Deficiency 1: **Dissolution testing should be conducted on 12 individual test and reference tablets used in the bioequivalence studies. Dissolution profiles should be generated in aqueous media of four different pH ranges as described in 'Guidance: Oral Extended (controlled) Release Dosage Forms *In Vivo* Bioequivalence And *In Vitro* Dissolution Testing'. Please follow the general dissolution conditions as described in this guidance.**

Response: The dissolution data on test and reference tablets in water, 0.1N HCl pH 1.25, sodium acetate buffer pH 4.5, and potassium phosphate buffer pH 6.4 are provided. The tests were conducted in 900 mL of appropriate media using apparatus 2 (paddles) at 50 and 75 rpm. Similar dissolution profiles were seen for test and reference tablets in all the media. The increase in paddle speed from 50 rpm to 75 rpm had little effect on drug release. The dissolution was faster in 0.1N HCl.

Deficiency 2: **In the informed consent form, vol. 1.2 pages 132-138, page 1 names orphenadrine citrate tablets and Norflex® tablets as the test and reference drugs; while page 2 states that test drug will be glyburide (Invamed) and the reference drug will be Glynase (Upjohn). Pages 2 to 7 of the consent form do not appear to belong to this study. Approved by the NIIRB on 9/10/96 is written at the bottom of each page of this informed consent. Please clarify.**

Response: During compilation of the final study report, pages 2-7 from a different protocol were inadvertently inserted behind page 1 of the informed consent form. A revised informed consent form is attached in the amendment.

Comment: Response is acceptable.

Deficiency 3: **Chromatograms: We note that though the sample peaks are larger than the internal standard peaks, they have lower integrated height numbers (e.g. page 300 vol. 1.2: the sample peak height is only 29,422 compared with the internal standard peak at 114,767 whereas sample peak appears about 1.5 times bigger than internal standard peak). Please clarify. Was the attenuator setting changed between the two peaks during the run? If yes, how would it affect the baseline and calculation of analyte to internal standard peak ratio? In some runs, it forms new baseline after the elution of internal standard (and change in attenuator setting?); e.g. pages 1118-1123, vol. 1.3. Please describe in detail what exactly was done.**

Response: Fasting Study: The integrator setting contained a difference in attenuation occurring at 7.50 minutes (an attenuation change from and the pen was zeroed at 7.60 minutes. This setting was established pre-run and was used for each following injection. The measurements of peak height is unaffected by changes in attenuation and pen placement. Therefore, the baseline and calculation of analyte to internal standard peak ratio are unaffected.

Comment: Response is acceptable.

Deficiency 4: **Please submit all SOP's for analytical methods.**

Response: The SOP's are attached in the amendment.

Deficiency 5: **Please explain why plasma orphenadrine concentrations were undetectable in subject #9, period II, food study.**

Response: The firm is unable to provide any definitive explanation for this.

Comments:

1. There is no USP dissolution method for this drug product at this time. The submitted dissolution data are acceptable. The firm can conduct dissolution testing in 900 mL water using apparatus 2 (paddles) at 50 rpm (Table 1) for stability program. The interim specifications would be:

1 hour: %
4 hours: %
12 hours: NLT %

2. Food Study: Subject #9 had undetectable plasma orphenadrine concentrations in period II (test-fasting) for unknown reasons. However, this does not affect the outcome of the study since the test and reference drugs are compared only under non-fasting conditions in this study.

3. Currently, DBE does not require a multiple-dose study for approval of this drug product.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Kiel Laboratories on its orphenadrine citrate extended release 100 mg tablets, lot #GA185, comparing it to the reference product Norflex® 100 mg tablets, lot #951362 manufactured by 3M Pharmaceuticals is acceptable to the Division of Bioequivalence. The study demonstrates that Kiel's orphenadrine citrate extended release 100 mg tablet is bioequivalent to the reference product, Norflex® 100 mg tablet manufactured by 3M.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Kiel Laboratories on its orphenadrine citrate extended release 100 mg tablets, lot #GA185, comparing it to the

reference product Norflex® 100 mg tablets, lot #951362 manufactured by 3M Pharmaceuticals is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Kiel's orphenadrine citrate extended release 100 mg tablet is similar to that of the reference product, Norflex® 100 mg tablet manufactured by 3M.

3. The dissolution testing conducted by the firm on its orphenadrine extended release tablets is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL water at 37°C using USP 23 apparatus II (paddles) at 50 rpm. The test product should meet the following interim specifications:

1 hour: %
4 hours: %
12 hours: NLT %

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

/S/ 7/31/98
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 8/4/98

Concur: /S/ Date 10/19/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Draft: 072498; Final: 073198

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Orphenadrine Citrate ER Tablets
Dose Strength: 100 mg
ANDA No.: 40-249
Firm: Kiel Laboratories
Submission Date: March 26, 1998
File Name: 40249SD.398

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications:
Reference Drug: Norflex® (3M)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hour)	Test Product Lot # GA185 Strength(mg) 100			Reference Product Lot # 951362 Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
1	35		3.4	29		3.4
2	47		3.3	39		2.3
4	63		3.4	53		2.4
6	72		2.9	63		2.3
8	80		2.4	69		2.1
10	82		1.6	76		2.2
12	86		1.7	81		2.2

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

AUG 5 1997

Orphenadrine Citrate Tablets, 100 mg Extended-Release
ANDA #40-249
Reviewer: Kuldeep R. Dhariwal
File name: 40249SD.297

Kiel Laboratories, Inc.

2225 Centennial Drive
Gainesville
Georgia 30504
Submission Date:
February 17, 1997

Review of Fasting and Non-Fasting Study and Dissolution Data

The firm has submitted *in vivo* bioequivalence studies under fasting and non-fasting conditions and dissolution data comparing its orphenadrine citrate extended release tablets, 100 mg with Norflex® (3M Pharmaceuticals).

Introduction:

Orphenadrine citrate is the citrate salt of orphenadrine (2-dimethyl 2-methylbenzhydryl ether citrate). It is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions. The mode of action of the drug has not been clearly identified, but may be related to its analgesic properties.

The reference listed drug is Norflex® by 3M and is available as 100 mg tablet and injection (2 mL ampuls containing 60 mg of orphenadrine citrate). Norflex® extended-release tablets provide 12 hours relief from the pain. The usual adult dose is two tablets per day-one in the morning and one in the evening.

Bioavailability of Orphenadrine Citrate Extended-Release Tablets, 100 mg under Fasting Conditions:

A. Objective:

To determine the bioequivalence of orphenadrine citrate extended release tablets, 100 mg made by Kiel Laboratories, Inc., relative to the listed drug product, Norflex® tablets, 100 mg made by 3M Pharmaceuticals, in healthy, normal males under fasting conditions.

B. Study Sites and Investigators:

Clinical and Analytical Site:
Principal Investigator:
Director, Analytical Lab:
Protocol # KEN-601 `Single-dose two-way crossover bioequivalence study of orphenadrine citrate extended release tablets and Norflex® tablets in healthy male volunteers' was approved by the

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 132, vol. 1.2.
Study Dates: Period I September 15-20, 1996
Period II September 29 - October 4, 1996
Analysis Dates: October 7 to October 23, 1996

C. Study Design:

The study was a randomized, single-dose, two-way crossover with two weeks wash out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours postdose each period. Subjects returned to the facility for 36, 48, 72, and 96 hour blood samples. The subjects were assigned as follows:

Subject #	Period I	Period II
1,3,4,9,12,13,15,17,18,20	A	B
2,5,6,7,8,10,11,14,16,19	B	A

Subject #5 did not complete the study.

A= Orphenadrine citrate extended release tablets, 1x100 mg, Kiel Laboratories; Lot #GA185; Batch size: theoretical actual yield tablets; Assay: %; Uniformity of Dosage Units: %; Manufacture date: April 9, 1996

B= Norflex® tablets, 1x100 mg; 3M Pharmaceuticals; Lot # 951362; Assay: %; Uniformity of Dosage Units: %; Expiry Date: January 1999

Formulation of the test product is given in Table 1.

The subjects fasted for no fewer than 10 hours prior to dosing and 4 hours after drug administration. Water was not allowed within one hour of drug administration. The drug products were dosed with 240 mL of water. The subjects were dosed at 1 minute interval and remained sitting upright or standing for 4 hours. Identical meals were served during both periods. Blood pressure and pulse measurements were obtained predose, 2 hours postdose, and prior to release in each study period. A physical examination was performed prior to release in period II.

D. Subject Selection:

Twenty healthy male subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-40 years of age
- weight within 15% of ideal body weight
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from the study based on the following criteria:

- significant history or current evidence of gastrointestinal, chronic infectious disease, system disorder or organ dysfunction
- history of alcohol or drug abuse
- participation in another clinical study within 4 weeks of study start
- allergic or hypersensitive to a component of orphenadrine citrate tablets

Subjects were imposed with following restrictions:

- no prescription drugs within 7 days or OTC medications within 72 hours of the drug administration, each period. No medications during confinement period
- no products containing alcohol or caffeine for 48 hours before and 96 hours after each dosing and throughout confinement
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Blood samples were collected in evacuated tubes containing potassium oxalate and sodium fluoride as an anticoagulant at 0 (predose), 1,2,3,3.5,4,5,6,8,10,12,16,24,36,48,72, and 96 hours. Blood was centrifuged to separate the plasma which was immediately decanted and frozen at -17°C.

F. Analytical Methods:

ACCEPTANCE CRITERIA: The analyte run was considered acceptable if 4 out of 6 control samples processed with each sample set were within % of their nominal concentration for 50 and 100 ng/mL orphenadrine control samples and % of the nominal concentration for the 6 ng/mL orphenadrine control samples. Also, one control sample at each concentration must have been within the above specified range.

G. Pharmacokinetics/Statistics:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C_t). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C_t/KE. The elimination rate constant (KE) was estimated as the absolute value of the slope of the regression line for the terminal log-linear concentration-time values. The values included in the regression analyses were determined by examination of the individual subject plots of natural logarithm of concentration against time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using GLM procedure of the SAS statistical program. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals for pair-wise area peak concentration comparisons were calculated by the t-test approach (2,1-sided).

H. Results:

1. Clinical:

Twenty subjects entered the study. Subject #5 was withdrawn at period II check-in because of a positive urine drug test. Nineteen subjects completed the study.

Adverse events:

Five subjects experienced adverse events like diarrhea, headache, drowsiness, and upset stomach. None of them required any medications.

Deviations in the study:

Following deviations in scheduled phlebotomy times have been reported:

Subject #	Period	Product	Sampling Time	Deviation
4	II	Ref	36 h	13 min late
5	I	Ref	48 h	130 min late
			96 h	No sample
9	I	Test	96 h	4 min late
	II	Ref	72 h	58 min late
			96 h	5 min late
10	II	Test	48 h	48 min late
15	I	Test	1 h	4 min late
			48 h	No sample
			96 h	No sample
	II	Ref	48 h	No sample
			72 h	6 min late
			96 h	6 min late
16	I	Ref	96 h	No sample
18	I	Test	1 h	3 min late
	II	Ref	1 h	2 min late
20	II	Ref	3.5 h	1 min late

Note: Actual sampling times were used for pharmacokinetic parameter calculations.

Reassays:

Three samples were reassayed due to bad chromatography. Two samples were reassayed due to incomplete processing. All samples from subject #7 and 8 were reanalyzed due to error in processing.

2. Analytical:

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of orphenadrine at each time point after test and reference products are shown in Table 2. The time courses of orphenadrine concentrations after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table 2. AUC_{0-t} and AUC_{0-inf} of the test product were 1 and 2% respectively lower than that of the reference product. The C_{max} of the test product was 2% lower and occurred 1 hour earlier. Subject #15 had missing 48 and 96 hours samples in period I and 48 hour sample in period II; therefore elimination constant and AUC_{0-inf} was not calculated for this subject.

The individual test/reference ratio for AUC_{0-t} ranged from (mean 1.03), AUC_{0-inf} ranged from (mean 0.99) and for C_{max} ranged from with a mean of 1.00 (Table 3).

The AUC_{0-t}/AUC_{0-inf} ratios range from for test and for reference product (Table 4).

The 90% confidence intervals for AUC and C_{max} are within the acceptable limits of % (Table 2). Statistical analysis of the data show significant period effect for AUC_{0-inf} (p value 0.0192 and $LAUC_{0-inf}$ (p value 0.0432).

Bioavailability of Orphenadrine Citrate ER Tablets, 100 mg: Non-Fasting Study

A. Objective: To determine the relative bioavailability of orphenadrine citrate extended release tablets made by Kiel Laboratories relative to the Norflex® tablets made by 3M in healthy adult males under non-fasting conditions and to assess the effect of food on the bioavailability of the test tablet.

B. Study Sites and Investigators:

Clinical and Analytical Site:
Principal Investigator:
Protocol #9631402B `The Effect of Food on the Bioavailability of Orphenadrine Tablets' was approved by the

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 726, vol. 1.3.
Study Dates: Period I June 8, 1996
Period II June 15, 1996
Period III June 22, 1996
Analysis Dates: June 26 to July 12, 1996

C. Study Design:

This was a randomized, single oral dose, three-treatment, three-period, six sequence crossover study with a one week washout period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours after drug administration. The subjects returned to the clinical facility for 36, 48, 60, and 72 hour blood draw. The subjects were assigned as follows:

Subject #	Period I	Period II	Period III
2,9,18,19	A	B	C
1,5,13	C	B	A
3,7,15	A	C	B
4,14,17,21	C	A	B
6,10,11	B	A	C
8,12,16,20	B	C	A

Subject #14 did not complete the study

A= Orphenadrine citrate extended release tablet, 1x100 mg following a standard meal; Kiel Laboratories; Lot #GA185

B= Orphenadrine citrate extended release tablet, 1x100 mg following an overnight fast; Kiel Laboratories; Lot #GA185

C= Norflex® extended release tablet, 1x100 mg following a standard meal; 3M Pharmaceuticals; Lot #951362

Lot numbers of the drug products administered in this study are the same as those used for the fasting study.

D. Subject Selection:

Twenty-one healthy male subjects were enrolled in the study with essentially same inclusion and exclusion criteria as used for fasting study.

E. Study Procedure:

Treatments A and C: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2 oz. of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered within 15 minutes after the start of breakfast and was given with 240 mL of water.

Treatment B: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection:

Blood samples were collected in evacuated tubes containing potassium oxalate and sodium fluoride as an anticoagulant at 0 (predose), 1,2,3,4,5,6,8,10,12,15,18,24,36,48,60, and 72 hours. Blood was centrifuged to separate the plasma which was immediately decanted and frozen at -20°C.

G. Analytical Methods, Pharmacokinetics/Statistics:

Same as for fasting study.

H. Results:

1. Clinical:

Twenty subjects out of twenty-one enrolled completed the study. Subject #14 was withdrawn at check-in of period III because of a positive urine drug test. Eight subjects experienced adverse events like headache, drowsiness, diarrhea, tooth ache, and jaw pain. None of the events required any medications.

Deviations in the study:

1. Samples from subject #2 were processed using an increased concentration of internal standard, due to the presence of a significant interference at its retention time in period II, predose sample. Method was validated using increased concentration of internal standard.

2. Following deviations in scheduled phlebotomy times were reported:

Subject #	Period	Product	Sampling time	Deviation
9	I	Test-fed	48 h	40 min late
			72 h	76 min late
12	I	Test-fast	60 h	8 min late
14	I	Ref-fed	48 h	76 min late
17	I	Ref-fed	60 h	no sample
19	I	Test-fed	36 h	3 min early
20	I	Test-fast	18 h	3 min late
1	II	Test-fast	72 h	33 min late
2	II	Test-fast	72 h	13 min late
3	II	Ref-fed	72 h	2 min late
5	II	Test-fast	5 h	2 min late
7	II	Ref-fed	5 h	2 min late
9	II	Test-fast	1 h	2 min late
			60 h	2 min late
	III	Ref-fed	24 h	3 min late
12	III	Test-fed	48 h	8 min late
15	III	Test-fast	60 h	3 min late

In addition, there were several (37) 1 minute deviations. Actual blood draw times were used for pharmacokinetic parameter calculations.

Reassays:

Eleven samples were reassayed due to bad chromatography and one sample was reassayed because its value was outside the standard curve range.

2. Analytical:

3. Pharmacokinetics/Statistics:

The concentration of orphenadrine measured at each time point after each product is summarized in Table 5. The time courses of orphenadrine concentration after the three treatments are plotted in Figure 2. The firm did not use the data of subject #2, period III (reference non-fasting) because of substantial interference in his predose sample (57.85 ng/mL).

Test formulation after a meal vs. reference formulation after a meal: The least squares means for AUC_{0-t} were % lower and that of AUC_{0-inf} were % lower than the reference formulation. The C_{max} of the test formulation was % lower than that of the reference product and occurred about 2 hours earlier.

Test formulation after a meal vs. test formulation after a 10 hour fast: The least squares means for AUC_{0-t} were % higher and for AUC_{0-inf} were % higher for test non-fasting compared to test fasting. The mean C_{max} was % higher and 10 minutes earlier in test non-fasting compared to the test fasting conditions.

The following are the ratios of the means of the pharmacokinetic parameters:

Test non-fasting/Ref non-fasting

Parameter	Ratio of Arithmetic means	Ratio of Geometric means
AUC_{0-t}	0.91	0.89
AUC_{0-inf}	0.95	0.93
C_{max}	0.87	0.86

Test non-fasting/Test fasting

AUC_{0-t}	1.03	0.98
AUC_{0-inf}	1.02	1.02
C_{max}	1.08	1.01

Subject #12 had measurable orphenadrine plasma levels at 0 h in period II (test non-fasting) and period III (reference non-fasting). Subject #18 had measurable orphenadrine plasma levels at 0 h in period II (test fasting). Subject #2 had measurable plasma orphenadrine levels at 0 h in period III (reference non-fasting). The reviewer repeated the data analysis after omitting these subjects (#12,18, and 2). The mean plasma concentration and pharmacokinetic parameters are given in tables 8 and 9. The following are the ratios of the means for the pharmacokinetic parameters for test non-fasting/reference non-fasting:

Parameter	Ratio of Arithmetic means	Ratio of Geometric means
AUC_{0-t}	0.89	0.88
AUC_{0-inf}	0.92	0.91
C_{max}	0.89	0.87

Dissolution:

There is no USP dissolution method for orphenadrine citrate ER tablets. The Division has a guidance for this product. However, the guidance is outdated (dated July 22, 1983). The firm conducted the dissolution testing in 900 mL water using apparatus II (paddle) at 50 rpm (Table 10).

Comments:

1. The bioequivalence study requirement guidance for orphenadrine citrate tablets issued by DBE in July 1983 is outdated. The current policy of the Division for this product is as follows: Two *in vivo* bioequivalence studies, one under fasting conditions and the other under non-fasting conditions are required. Multiple-dose study is not required for this product (see

Division File for this product).

2. **Not to be released under FOI**

Fasting study:

1. Nineteen of the twenty subjects enrolled completed the study. Subject #5 was withdrawn at period II check-in because of a positive urine drug test. Five subjects experienced adverse events like diarrhea, headache, drowsiness, and upset stomach. None of them required any medications.

2. AUC_{0-t} and AUC_{0-inf} of the test product were 1 and 2% respectively lower than that of the reference product. The C_{max} of the test product was 2% lower and occurred 1 hour earlier.

3. The 90% confidence intervals for AUC and C_{max} are within the acceptable limits of 80-125%. Statistical analysis of the data show significant period effect for AUC_{0-inf} (p value 0.0192 and $LAUC_{0-inf}$ (p value 0.0432).

4. There was a good agreement between reviewer's calculations and those provided by the firm.

Non-Fasting study:

1. Twenty subjects out of twenty-one enrolled completed the study. Subject #14 was withdrawn at check-in of period III because of a positive urine drug test. Eight subjects experienced adverse events like headache, drowsiness, diarrhea, tooth ache, and jaw pain. None of the events required any medications.

2. Subject #9 had no detectable plasma orphenadrine levels at any time point in period II (test-fast). The subject did not experience any adverse events and the firm has not provided any explanation for this.

3. The least squares means for AUC_{0-t} were 10% lower and that of AUC_{0-inf} were 6% lower in test non-fasting compared to reference non-fasting. The C_{max} of the test non-fasting was 12% lower than that of the reference non-fasting and occurred about 2 hours earlier.

4. The least squares means for AUC_{0-t} were 3% higher and for AUC_{0-inf} were 5% higher for test non-fasting compared to test fasting. The mean C_{max} was 8% higher and 10 minutes earlier in test non-fasting compared to the test fasting conditions.

5. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within acceptable limits.

6. Subject #12 had measurable orphenadrine plasma levels at 0 h in period II (test non-fasting) and period III (reference non-fasting). Subject #18 had measurable orphenadrine plasma levels at 0 h in period II (test fasting). Subject #2 had measurable plasma orphenadrine levels at 0 h in period III (reference non-fasting). The reviewer repeated the data analysis after omitting these subjects (#12,18, and 2). The ratio of means for AUC and C_{max} remained within acceptable limits.

Dissolution:

1. The dissolution testing conducted by the firm is not acceptable. The firm would be asked to perform dissolution testing in aqueous media at 4 different pH ranges as described in guidance for extended release dosage forms.

2. The orphenadrine citrate tablets are not scored and therefore dissolution testing on half tablets is not required.

Deficiencies:

1. Dissolution testing should be conducted on 12 individual test and reference tablets used in the bioequivalence studies. Dissolution profiles should be generated in aqueous media of four different pH ranges as described in `Guidance: Oral Extended (controlled) Release Dosage Forms *In Vivo* Bioequivalence And *In Vitro* Dissolution Testing'. Please follow the general dissolution conditions as described in this guidance.

2. Informed consent; vol.1.2 pages 132-138: Page 1 of this informed consent states orphenadrine citrate tablets and Norflex® tablets as test and reference drugs. Page 2 states that test drug will be glyburide (Invamed) and the reference drug will be Glynase (The Upjohn). Pages 2 to 7 of the consent form do not appear to belong to this study. Approved by the NIIRB on 9/10/96

is written at the bottom of each page of this informed consent. Please clarify.

3. Chromatograms: One finds that sample peaks larger than the internal standard peaks have lower integrated height numbers than internal standard peaks (e.g. page 300 vol.1.2: sample peak is only 29,422 compared to internal standard peak 114,767 whereas sample peak is about 1.5 times bigger than internal standard peak). Please clarify. Was the attenuator setting changed between the two peaks during the run? If yes, how would it affect the baseline and calculation of analyte to internal standard peak ratio? In some runs, it forms new baseline after the elution of internal standard (and change in attenuator setting?); e.g. pages 1118-1123, vol. 1.3. Please describe in detail what exactly was done.

4. Please submit all SOPs for analytical methods.

5. Please explain why plasma orphenadrine concentrations were undetectable in subject #9, period II, food study.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Kiel Laboratories on its orphenadrine citrate extended release 100 mg tablets, lot #GA185, comparing it to the reference product Norflex® 100 mg tablets, lot #951362 manufactured by 3M Pharmaceuticals has been found incomplete by the Division of Bioequivalence for the reasons given in the deficiencies.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Kiel Laboratories on its orphenadrine citrate extended release 100 mg tablets, lot #GA185, comparing it to the reference listed drug Norflex® 100 mg tablets, lot #951362 manufactured by 3M has been found incomplete by the Division of Bioequivalence for the reasons given in the deficiencies.

3. The dissolution testing conducted on orphenadrine citrate extended release 100 mg tablets is not acceptable. The firm is advised to repeat the dissolution testing as described in the DBE guidance of extended release tablets.

4. From bioequivalence point of view, the application is incomplete.

The firm may be informed of the deficiencies.

/S/ 8/5/97

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

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 8/5/97

cc: ANDA #40-249 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), HFD-650 (Director), Drug File, Division File

Draft: 080197; Final: 080597

Table 1

Quantitative Composition of Orphenadrine Citrate ER Tablets

Ingredient	mg/tablet
Orphenadrine Citrate, USP	100.0
Calcium Stearate, USP	
Lactose, USP	
Ethylcellulose, USP	

TABLE 2

MEAN PLASMA ORPHENADRINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN FASTING STUDY (n=19): ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.93	3.23	1.07	2.66	1.81
2	15.70	7.20	15.09	6.74	1.04
3	25.82	8.52	24.94	8.47	1.04
3.5	29.53	8.74	28.31	9.56	1.04
4	32.02	8.84	30.87	10.39	1.04
5	37.78	9.24	36.47	9.38	1.04
6	38.21	8.84	36.76	10.23	1.04
8	35.50	8.59	35.41	9.94	1.00
10	32.69	9.15	33.86	9.32	0.97
12	33.19	9.39	36.11	9.25	0.92
16	29.92	8.79	33.68	9.67	0.89
24	27.44	8.28	27.98	8.44	0.98
36	17.51	5.92	17.89	6.11	0.98
48	12.08	4.73	11.97	5.07	1.01
72	5.67	4.06	5.39	4.54	1.05
96	1.92	2.93	1.95	2.94	0.99

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1591.62	1636.94	0.97	90.57	103.89
AUCT	1412.67	1427.50	0.99	90.38	107.54
CMAX	39.60	40.36	0.98	90.36	105.84
TMAX	7.57	8.58	0.88	--	--
LAUCI	1510.96	1546.17	0.98	91.45	104.43
LAUCT	1343.04	1338.33	1.00	91.40	110.18
LCMAX	38.57	39.13	0.99	91.35	106.37

1= Test
2= Reference

CI 12= Confidence Interval Test-Reference

UNIT: AUC=ng/mLxh CMAX=ng/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

TABLE 3

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS
IN FASTING STUDY

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	1	0.88	0.89	0.91	0.83	1.07	.
2	2	2	0.99	1.00	0.92	0.50	0.99	.
3	1	1	1.01	1.00	1.19	1.00	1.06	.
4	1	1	0.70	0.77	0.67	2.00	1.19	.
6	2	2	1.49	1.48	0.76	1.20	0.77	.
7	2	2	1.05	1.08	1.00	1.20	0.90	.
8	2	2	0.85	0.88	0.77	0.75	0.91	.
9	1	1	0.74	0.77	0.96	1.00	1.14	.
10	2	2	1.01	1.03	1.00	0.50	0.96	.
11	2	2	1.08	1.08	1.03	1.00	1.01	.
12	1	1	1.01	1.03	1.15	1.00	0.89	.
13	1	1	0.97	0.95	1.09	1.00	1.06	.
14	2	2	1.16	1.15	1.27	1.33	1.04	.
15	1	1	1.71	.	1.15	0.50	.	.
16	2	2	0.99	0.94	1.27	0.42	1.16	.
17	1	1	1.32	1.21	1.12	0.83	0.80	.
18	1	1	0.88	0.89	0.87	1.00	0.97	.
19	2	2	1.02	1.02	1.10	2.00	0.93	.
20	1	1	0.68	0.69	0.78	0.31	0.87	.

UNIT: AUC=ng/mLxh CMAX=ng/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	19	1.03	0.26	0.68	1.71
RAUCI12	18	0.99	0.18	0.69	1.48
RCMAX12	19	1.00	0.18	0.67	1.27
RTMAX12	19	0.97	0.46	0.31	2.00
RKE12	18	0.98	0.12	0.77	1.19
RTHALF12	0	.	.	.	.

1= TEST
2= REFERENCE

TABLE 4

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS
IN FASTING STUDY

OBS	SUB	TRT	AUCRATIO
1	1	1	0.88
2	2	1	0.91
3	3	1	0.80
4	4	1	0.87
5	6	1	0.95
6	7	1	0.89
7	8	1	0.87
8	9	1	0.92
9	10	1	0.92
10	11	1	0.91
11	12	1	0.92
12	13	1	0.87
13	14	1	0.96
14	15	1	.
15	16	1	0.89
16	17	1	0.88
17	18	1	0.88
18	19	1	0.88
19	20	1	0.87
20	1	2	0.89
21	2	2	0.92
22	3	2	0.80
23	4	2	0.95
24	6	2	0.94
25	7	2	0.91
26	8	2	0.89
27	9	2	0.95
28	10	2	0.93
29	11	2	0.91
30	12	2	0.94
31	13	2	0.85
32	14	2	0.95
33	15	2	.
34	16	2	0.85
35	17	2	0.81
36	18	2	0.89
37	19	2	0.89
38	20	2	0.89

STATISTICS ON AUCT/AUCI RATIOS

	N	Mean	Std Dev	Minimum	Maximum
TRT 1 (TEST)	18	0.89	0.04		

	N	Mean	Std Dev	Minimum	Maximum
TRT 2 (REFERENCE)	18	0.90	0.05		

Table 5

MEAN PLASMA ORPHENADRINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY (n=20)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.16	0.73	0.17	0.77	0.16	0.70	0.94
1	2.40	3.79	2.11	3.00	1.11	3.06	1.14
2	17.43	7.94	17.74	10.50	13.16	7.65	0.98
3	29.96	13.42	29.57	11.99	27.69	12.86	1.01
4	38.46	16.76	37.26	14.44	37.04	15.57	1.03
5	44.54	19.17	48.52	21.97	50.82	17.46	0.92
6	44.73	19.06	47.36	21.77	52.93	19.31	0.94
8	40.52	16.05	42.55	19.20	50.92	19.09	0.95
10	37.73	15.43	37.62	15.80	50.37	18.35	1.00
12	36.23	13.47	33.52	14.80	49.68	18.07	1.08
15	36.10	14.81	32.26	16.13	46.30	14.96	1.12
18	33.46	15.26	31.18	16.01	40.29	12.70	1.07
24	30.92	13.10	28.85	12.90	35.38	13.78	1.07
36	21.02	10.61	22.40	9.90	21.38	9.50	0.94
48	15.71	8.69	18.02	9.52	15.93	9.30	0.87
60	9.77	5.88	11.55	7.34	10.46	6.98	0.85
72	6.79	5.49	9.04	6.39	7.86	5.89	0.75

(CONTINUED)

UNIT: PLASMA LEVEL=ng/mL TIME=HRS
MEAN PLASMA ORPHENADRINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	1.01	1.07
1	2.17	1.90
2	1.32	1.35
3	1.08	1.07
4	1.04	1.01
5	0.88	0.95
6	0.85	0.89
8	0.80	0.84
10	0.75	0.75
12	0.73	0.67
15	0.78	0.70
18	0.83	0.77
24	0.87	0.82
36	0.98	1.05
48	0.99	1.13
60	0.93	1.10
72	0.86	1.15

1= TEST-FAST
2= TEST-NON-FASTING
3= REF-NON-FASTING

TABLE 6

ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1956.89	832.94	1990.84	1009.25	2099.36	989.87	0.98
AUCT	1576.31	704.01	1622.82	703.08	1792.61	738.12	0.97
CMAX	46.68	19.28	50.38	21.39	57.76	19.64	0.93
KE	0.03	0.01	0.03	0.01	0.03	0.01	1.07
LAUCI	1806.12	0.41	1786.61	0.47	1909.94	0.44	1.01
LAUCT	1560.40	0.36	1493.96	0.42	1667.38	0.38	1.04
LCMAX	47.03	0.29	46.77	0.38	54.68	0.34	1.01
THALF	22.21	5.40	23.79	6.40	22.69	5.93	0.93
TMAX	6.11	1.73	6.05	3.05	8.00	3.60	1.01

(CONTINUED)

UNIT: AUC=ng/mLxh CMAX=ng/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.93	0.95
AUCT	0.88	0.91
CMAX	0.81	0.87
KE	1.01	0.95
LAUCI	0.95	0.94
LAUCT	0.94	0.90
LCMAX	0.86	0.86
THALF	0.98	1.05
TMAX	0.76	0.76

1= TEST-FASTING
2= TEST-NON-FASTING
3= REFERENCE-NON-FASTING

TABLE 7

LSMEANS AND RATIOS IN NON-FASTING STUDY

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1907.27	1992.66	2110.76	0.96	0.90	0.94
AUCT	1585.61	1629.91	1810.67	0.97	0.88	0.90
CMAX	46.90	50.69	57.75	0.93	0.81	0.88
LAUCI	1762.39	1794.71	1937.90	0.98	0.91	0.93
LAUCT	1528.32	1502.18	1689.89	1.02	0.90	0.89
LCMAX	46.37	47.05	54.56	0.99	0.85	0.86

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

	LSM1	LSM2	LSM3	LOWCI12	UPPCI12	LOWCI13	UPPCI13
PARAMETER							
AUCI	1907.27	1992.66	2110.76	87.02	104.41	82.15	98.57
AUCT	1585.61	1629.91	1810.67	88.53	106.03	79.70	95.44
CMAX	46.90	50.69	57.75	80.53	104.50	70.68	91.73
LAUCI	1762.39	1794.71	1937.90	90.73	106.28	84.03	98.43
LAUCT	1528.32	1502.18	1689.89	94.35	109.71	83.87	97.52
LCMAX	46.37	47.05	54.56	89.08	109.04	76.82	94.05

(CONTINUED)

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

	LOWCI23	UPPCI23
PARAMETER		
AUCI	86.20	102.61
AUCT	82.14	97.89
CMAX	77.25	98.29
LAUCI	85.57	100.24
LAUCT	82.43	95.86
LCMAX	77.95	95.42

1= TEST-FASTING
2= TEST-NON-FASTING
3= REFERENCE-NON-FASTING

TABLE 8

MEAN PLASMA ORPHENADRINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY
AFTER OMITTING SUBJECTS WITH 0 HOUR DRUG LEVELS (#2, 12, AND 18)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
1	2.61	4.02	1.81	3.17	1.05	3.19	1.44
2	16.87	7.92	17.48	10.92	12.94	7.80	0.97
3	27.55	11.37	28.84	12.11	26.92	13.27	0.96
4	34.90	13.38	36.99	15.61	35.69	15.55	0.94
5	40.19	14.54	47.33	21.70	49.05	17.64	0.85
6	40.02	13.66	46.61	21.42	50.64	18.25	0.86
8	37.57	14.34	41.46	19.30	47.88	17.33	0.91
10	33.44	11.64	36.51	16.00	48.90	17.94	0.92
12	33.83	12.76	32.17	15.03	48.27	17.84	1.05
15	32.95	12.79	31.71	16.94	44.70	14.49	1.04
18	29.78	12.19	30.48	16.96	38.33	11.89	0.98
24	28.99	13.09	27.09	13.03	33.59	13.44	1.07
36	18.64	9.38	19.88	8.09	19.90	8.90	0.94
48	13.71	7.47	15.60	7.63	14.32	8.43	0.88
60	8.56	5.16	9.69	5.71	9.32	6.45	0.88
72	5.33	4.27	7.42	4.98	6.68	4.99	0.72

(CONTINUED)

UNIT: PLASMA LEVEL=ng/mL TIME=HRS
MEAN PLASMA ORPHENADRINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
1	2.49	1.73
2	1.30	1.35
3	1.02	1.07
4	0.98	1.04
5	0.82	0.96
6	0.79	0.92
8	0.78	0.87
10	0.68	0.75
12	0.70	0.67
15	0.74	0.71
18	0.78	0.80
24	0.86	0.81
36	0.94	1.00
48	0.96	1.09
60	0.92	1.04
72	0.80	1.11

1= TEST-FASTING
2= TEST-NON-FASTING
3= REFERENCE-NON-FASTING

TABLE 9

ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY AFTER OMITTING SUBJECTS
WITH 0 HOUR DRUG LEVELS (#2, 12, AND 18)

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	1739.15	642.93	1772.44	853.85	1923.37	883.59	0.98
AUCT	1417.60	606.71	1498.71	663.42	1684.51	701.86	0.95
CMAX	41.89	14.41	49.19	21.21	55.50	19.10	0.85
KE	0.03	0.01	0.03	0.01	0.03	0.01	1.07
LAUCI	1639.34	0.35	1621.16	0.42	1773.54	0.40	1.01
LAUCT	1436.55	0.31	1386.68	0.40	1574.92	0.36	1.04
LCMAX	43.53	0.22	45.66	0.38	52.60	0.34	0.95
THALF	21.02	4.44	22.29	4.27	21.34	4.41	0.94
TMAX	5.94	1.57	6.18	3.19	8.12	3.79	0.96

(CONTINUED)

UNIT: AUC=ng/mLxh CMAX=ng/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.90	0.92
AUCT	0.84	0.89
CMAX	0.75	0.89
KE	1.02	0.95
LAUCI	0.92	0.91
LAUCT	0.91	0.88
LCMAX	0.83	0.87
THALF	0.98	1.04
TMAX	0.73	0.76

UNIT: AUC=ng/mLxh CMAX=ng/mL TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	1639.77	1723.59	1879.89	0.95	0.87	0.92
AUCT	1371.53	1454.98	1643.16	0.94	0.83	0.89
CMAX	40.67	48.24	54.24	0.84	0.75	0.89
LAUCI	1541.46	1568.32	1725.82	0.98	0.89	0.91
LAUCT	1358.72	1345.40	1535.04	1.01	0.89	0.88
LCMAX	41.90	44.89	51.44	0.93	0.81	0.87

1= TEST-FASTING
2= TEST-NON-FASTING
3= REFERENCE-NON-FASTING

Table 10. In Vitro Dissolution Testing

Drug (Generic Name): Orphenadrine Citrate ER
Dose Strength: 100 mg
ANDA No.: 40-249
Firm: Kiel Laboratories
Submission Date: February 17, 1997
File Name: 40249SD.297

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications:
Reference Drug: Norflex (3M)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Hour)	Test Product Lot # not identified Strength(mg)			Reference Product Lot # not identified Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
1	29.9		2.4	30		2.5
2	40.6		2.4	46		3.2
4	54.8		2.6	64		2.3
6	64.3		2.2	73		1.5
8	71.0		2.1	80		2.3
10	76.3		2.4	88		1.9
12	81.0		1.7	92		2.8

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

IG P–1. PLASMA ORPHENADRINE LEVELS

ORPHENADRINE CITRATE TABLETS, 100 MG, ANDA #40-249
UNDER FASTING CONDITIONS
DOSE=1 X 100 MG

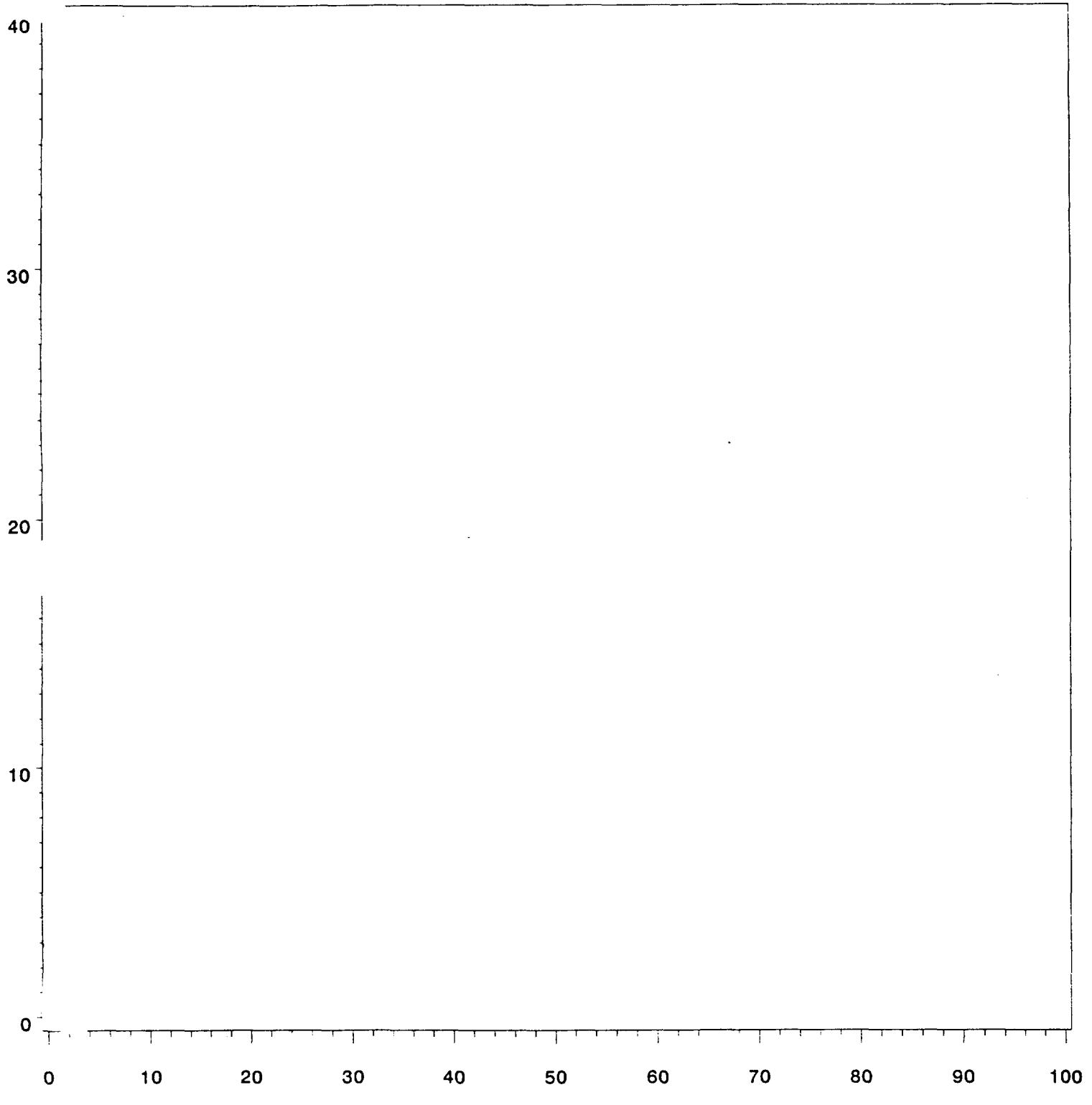


FIG P-2. PLASMA ORPHENADRINE LEVELS

ORPHENADRINE CITRATE ER TABLETS, 100 MG, ANDA #40-249
UNDER NONFASTING CONDITIONS
DOSE=1 X 100 MG

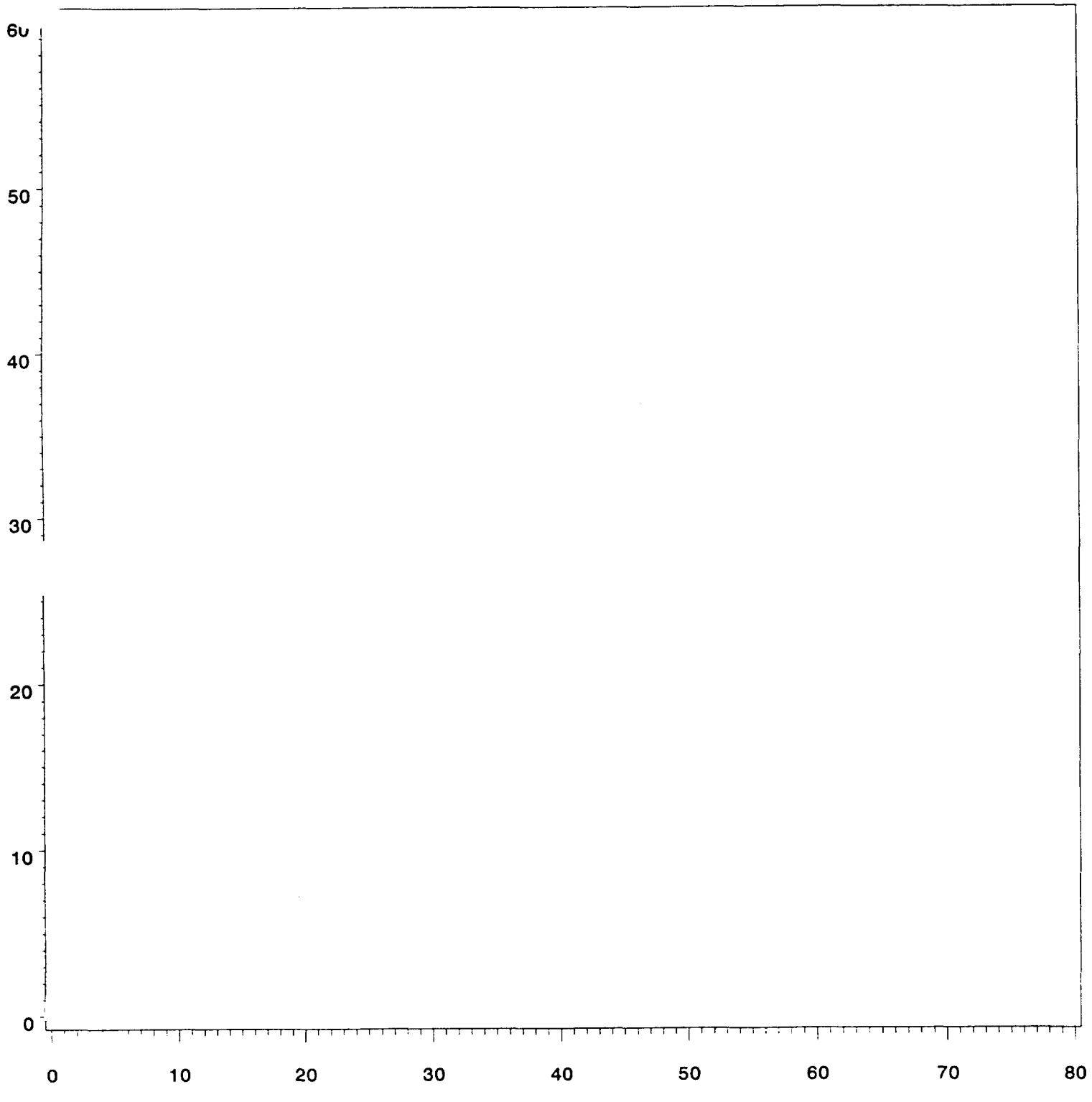
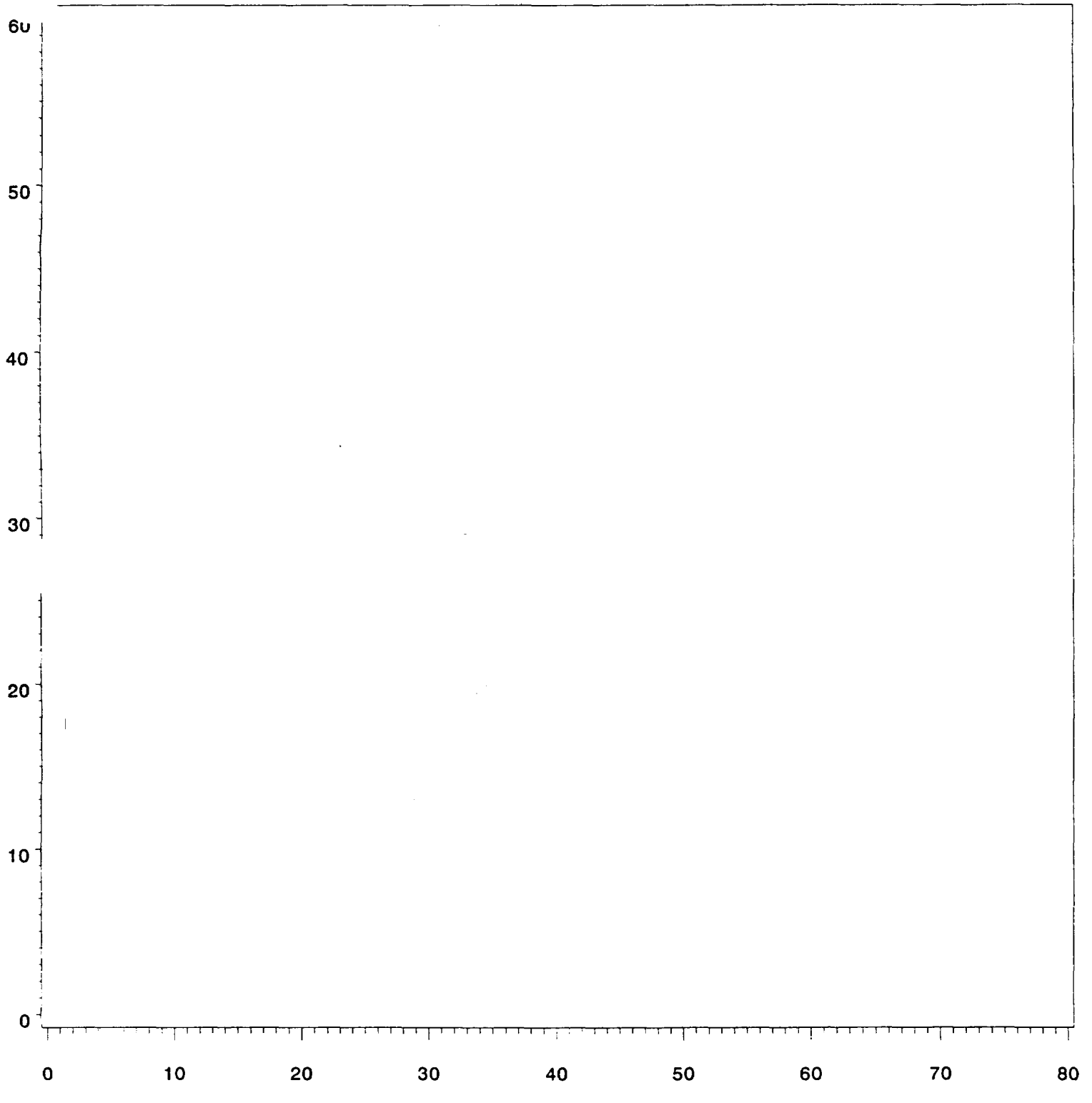


FIG P–2. PLASMA ORPHENADRINE LEVELS

ORPHENADRINE CITRATE ER TABLETS, 100 MG, ANDA #40-249
UNDER NONFASTING CONDITIONS
DOSE=1 X 100 MG



after omitting subjects 2, 12 and 18