CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-326

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-326 APPLICANT: Eon Laboratories

DRUG PRODUCT: Ticlopidine HCL

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 37^0 C using U.S.P. Apparatus (II) at 50 rpm. The test product should meet the following specifications:

I [redacted] in
t

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Ticlopidine **ANDA #**: 75-326
SPONSOR: Eon Lab
DOSAGE FORM: Tablet **STRENGTH**: 250mg
TYPE OF STUDY: Single dose, fasting and non-fasting.
STUDY SITE:
CLINICAL:
ANALYTICAL

STUDY SUMMARY:

Fasting: 2-way cross over in 44 subjects. 90% C.I. limits for LAUCt, LAUCinf and LCmax are within acceptable ranges.

Non-Fasting: 3-way cross over in 18 subjects. Least squares mean ratio of the Test (fed)/Ref (fed) is within acceptable range.

DISSOLUTION: USP XXII, Paddle, 50 RPM
Medium: Water, 900 ml at 37°C.
Specification:

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. **BRANCH**: II

INITIAL: /S/ DATE: 10/13

TEAM LEADER: Srinivas Nerurkar, Ph.D. **BRANCH**: II

INITIAL: /S/ DATE: 10/20/1998

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

INITIAL: /S/ DATE: 10/28/98

Ticlopidine Hydrochloride
Tablets, 250 mg
ANDA: #75-326
Reviewer: Nhan L. Tran
75326A.798

Eon Laboratories
Laurelton, NY
Submission Date:
July 21, 1998

Review of An Amendment

I. OBJECTIVE:

The firm has conducted two studies to compare the relative bioavailability of the test and reference ticlopidine formulations when given under fasting and fed conditions in healthy, adult, male subjects. The studies were reviewed on July 6, 1998 and were found deficient.
The present submission contains the responses from the firm to the deficiencies cited in the review.

II. REVIEW OF THE RESPONSES

Deficiency 1: "For the fasting and non fasting studies, it is requested to use the last three or four data points in computing Kel for appropriate estimation of the elimination rate constants, and hence AUCinf. New data should be generated and submitted along with appropriate statistical results for evaluation".

Firm's Response: The Kel was recalculated with no more than the last three or four data points of the plasma concentration-time profiles for all subjects in both fasting and nonfasting studies. Results reported by the firm are summarized in Table 1.

The response is acceptable.

Deficiency 2. "For both studies, subjects with irregularities at the terminal phase of the plasma concentration-time plots (V-shaped or inverted V-shaped) should be deleted from statistical analysis of AUCinf. New data should be generated and submitted along with appropriate statistical results".

Firm's Response: The firm re-calculated Kel by deleting subjects with irregularities at the terminal phase of the plasma concentration-time profiles as follows:
For the fasting study: Only one subject (Subject #21, reference product) presented significant irregularities at the terminal phase (Table 1).
For the fed study: Three subjects [subject #8, treatments B (test, fed) and C (ref, fed), subject #10, treatments A (test, fast), B (test, fed) and C (ref, fed) and subject #12, treatment C (ref, fed)] presented significant irregularities at the terminal phase. Results reported by the firm are shown in Table 2 below:

Table 1: Fasting.

TREATMENT		
Variable	A=TEST (%CV) N=44	B=REF.(%CV) N=43
KEL(1/hr)	0.041 (44.5)	0.044 (37.4)
T1/2 (hr)	19.91 (39.6)	17.83 (36.1)
AUCInf	1942.1 (50.0)	1931.3 (49.6)
90% C.I LAUCInf 91.6% - 103.7%		

Table 2: Non-fasting.

TREATMENT			
Variable	A=TEST, FAST(%CV) N = 17	B=TEST, FED (%CV) N = 16	C=REF, FED.(%CV) N = 15
KEL (1/hr)	0.03018 (31.4)	0.02870 (28.1)	0.02966 (23.5)
T1/2	25.25 (32.9)	25.94 (26.9)	25.40 (40.5)
AUCinf	2615.0 (35.7)	2676.6 (32.6)	2644.1 (31.4)

The response is acceptable.

Deficiency 3. "For both studies, the subjects who had levels above the LOQ at time zero, should be deleted from all analyses. New data should be generated and submitted to the Agency for evaluation".

Firm's Response:

Fasting study: No non-zero pre-dose concentration was reported.

Non fasting study: Only 1 subject (subject #10, Treatment C (reference, fed) was reported. This subject was deleted and the ratio of the [Test, fed/Ref, fed] was within acceptable range (0.94).

The response is acceptable.

Deficiency 4. "Detected levels, although below LOQ, were seen in many subjects in both studies (fasting study, 12 subjects: # 6, 18, 25, 32, 41, 42, 10, 16, 17, 19, 21 and 36, and fed study, 14 subjects: # 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, and 18), and in addition, all events occurred in the second (fasting) or second and/or third (fed) period suggesting an incomplete washout time between period. Is the observed phenomenon in violation of the basic statistical assumption of a cross-over design? Complete documentation should be provided to explain the observed phenomenon".

Firm's Response: The firm indicated that there were subjects with pre-dose concentration in both studies. However, those pre-dose concentrations were insignificant as they represented less than 0.4% of the Cmax in both studies. The washout period was therefore deemed adequate and hence there was no violation of the basic assumption of the cross-over study design.

The response is acceptable.

Data Summary:

The reviewer has verified all data submitted to the Agency and found the FDA values and those from the firm are comparable. However, the FDA's results are reported as follows:

1. For the fasting study, the 90% confidence intervals for LnCmax (90.6% - 104.5%), LnAUC (91.5% - 104.3%) and LnAUCinf (91.0% - 103.3%) are within the acceptable limits of 80% - 125%.

2. For the non-fasting study, the ratio of test (fed) to reference (fed) least squares means for LnAUC (0.98), LnAUCinf (0.98) and LnCmax (1.05)are within 0.8 - 1.25.

3. The dissolution data is acceptable using the FDA method and

specification of NLT

Recommendations

1. The fasting bioequivalence study conducted by Eon on its 250 mg Ticlopidine Tablets, lots 970605 and the post-prandial study on the 250 mg Ticlopidine Tablets comparing them to Roche's Ticlid^{R} 250 mg tablets has been found to be acceptable by the Division of Bioequivalence. The studies demonstrate that Eon's 250 mg Ticlopidine Tablets, are bioequivalent to the reference products Ticlid^{R} 250 mg tablets manufactured by Roche.

2. The in-vitro dissolution testing conducted on the 250 mg strength (lot # 970605), is acceptable.

3.The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900mL of water at 37^{0}C using U.S.P. apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

/S/ 10/20/98

Nhan L. Tran, Ph.D.
Review Branch II
Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR /S/ Date: 10/20/1998

Concur: /S/ Date: 10/28/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-326 APPLICANT: Eon Laboratories

DRUG PRODUCT: Ticlopidine HCL

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 37^0 C using U.S.P. Apparatus (II) at 50 rpm. The test product should meet the following specifications:

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

CC:

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Endorsements: (Final with Dates)
HFD-655/ Reviewer 10/20/98
HFD-655/ Bio team Leader
HFD-650/ D. Conner 10/25/98

BIOEQUIVALENCY - ACCEPTABLE submission dates: January 30, 1998 (Orig)
July 21, 1998 (Amend.)

1. FASTING STUDY (STF) Strengths: 250 mg
Clinical: Outcome: AC
Analytical:

2. FOOD STUDY (STP) Strengths: 250 mg
Clinical: Outcome: AC
Analytical: a

Outcome Decisions: AC - Acceptable

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-326 APPLICANT: Eon Laboratories

DRUG PRODUCT: Ticlopidine HCL

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 U.S.P. Apparatus (II) at 50 rpm. The test product should meet the following specifications:

[redacted]

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

CC:

Endorsements: (Final with Dates)
HFD-655/ Reviewer /S/
HFD-655/ Bio team Leader /S/ 10/20/98
HFD-650/ D. Conner /S/ 10/23/98

BIOEQUIVALENCY - ACCEPTABLE submission dates: January 30, 1998 (Orig)
July 21, 1998 (Amend.)

1. **FASTING STUDY** (STF) Strengths: 250 mg
Clinical:
Analytical: **Outcome: AC**

2. **FOOD STUDY** (STP) Strengths: 250 mg
Clinical:
Analytical: **Outcome: AC**

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Outcome Decisions: **AC** - Acceptable

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

ORIG
N/AB

July 21, 1998

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Reference: ***Bioequivalency Amendment***
Ticlopidine Hydrochloride Tablets, 250 mg
ANDA 75-326

Dear Dr. Conner:

In response to your letter dated July 7, 1998 commenting on the bioequivalency study performed by we have included our response to the FDA deficiency letter for project Nos. 962024 and 962025 Ticlopidine Hydrochloride Tablets, 250 mg ANDA: 75-326 supplied by .

Also included is a diskette containing the data in ASCII format.

As per your request we have also included a copy of the letter dated July 7,1998.

We hope that our responses satisfactorily address the deficiencies noted in your letter. If you need further information or clarification, please do not hesitate to call me at (718) 276-8607 ext. 404.

Sincerely,
Eon Labs Manufacturing, Inc.

Eva Sultana Khan.
Eva Sultana Khan, M.S.
Regulatory Affairs Associate

RECEIVED
JUL 23 1998
GENERIC DRUGS

Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

NDA [illegible] AMENDMENT

N/A

June 24, 1998

Ms. Nancy Chamberlin
Division of Bioequivalence, HFD 650
Office of Generic Drugs
7500 Standish Place
Rockville, MD 20855

RE: Ticlopidine Tablets, 250 mg
ANDA 75-326
Diskette for Bioequivalence Fasting (962024) and Fed/Fasting (962025) Studies

Dear Ms. Chamberlin:

Enclosed please find two replacement diskettes, one for the bioequivalence fasting study (962024) which has the complete set of data for all 44 subjects and the other for the fed/fasting study (962025) containing the plasma concentration and pharmacokinetic data for this study, which could not be accessed in the previously submitted diskette.

If there are any questions regarding this submittal please do not hesitate to contact Patricia Kaufold (x 423) or myself (x 404) at (718) 276-8607.

Sincerely,
Eon Labs Manufacturing, Inc.

Eva Sultana Khan

Eva Sultana Khan, M.S.
Regulatory Affairs Associate

RECEIVED
JUN 25 1998
GENERIC DRUGS

cc: S. Ciganek
A. Mehta

JUL 7 1998

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA:75-326 APPLICANT: Eon Laboratories
DRUG PRODUCT: Ticlopidine HCL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting and non fasting studies, it is requested to use the last three or four data points in computing Kel for appropriate estimation of the elimination rate constants, and hence AUCinf. New data should be generated and submitted along with appropriate statistical results for evaluation.

2. For both studies, subjects with irregularities at the terminal phase of the plasma concentration-time plots (V-shaped or inverted V-shaped) should be deleted from statistical analysis of AUCinf. New data should be generated and submitted along with appropriate statistical results.

3. For both studies, the subjects who had levels above the LOQ at time zero, should be deleted from all analyses. New data should be generated and submitted for evaluation.

4. Detected levels, although below the LOQ, were seen in many subjects in both studies **(fasting study, 12 subjects: # 6, 18, 25, 32, 41, 42, 10, 16, 17, 19, 21 and 36, and fed study, 14 subjects: # 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, and 18)**, and in addition, all events occurred in the second (fasting) or second and third (fed) period suggesting an incomplete washout time between period. Is the observed phenomenon in violation of the basic statistical assumption of a cross-over design? Please explain.

5. Please submit all requested information in electronic format (SAS or ASCII format) along with a hard copy for evaluation. Please make sure that the diskette is not defective and contains complete data as requested.

Sincerely yours

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs, CDER.

JUL 7 1998

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA:75-326 APPLICANT: Eon Laboratories
DRUG PRODUCT: Ticlopidine HCL

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Sincerely yours

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs, CDER.

Ticlopidine Hydrochloride
Tablets, 250 mg
ANDA: #75-326
Reviewer: Nhan L. Tran
75326SD.198

Eon Laboratories
Laurelton, NY
Submission Date:
January 30, 1998

Review of Two Single-Dose Bioequivalence Studies Under Fasting and Non-Fasting Conditions and Dissolution Testing

INTRODUCTION:

Eon has submitted two single-dose bioequivalence studies conducted under fasting and non-fasting conditions, and dissolution testing for its test product, Ticlopidine HCl Tablets, 250 mg, and the reference listed product, Ticlid Tablets, 250 mg manufactured by Inc., which has been purchased by
Ticlopidine hydrochloride is a platelet aggregation inhibitor agent. It is freely soluble in water. Ticlopidine hydrochloride is rapidly absorbed following administration of a 250 mg single dose. An absorption of greater than 80% and peak plasma levels at about 2 hours has been reported (PDR, 1997).
Ticlopidine hydrochloride reversibly binds 98% to plasma proteins, primarily to serum albumin and lipoproteins.
Ticlopidine hydrochloride is considerably metabolized by the liver, therefore only trace amounts of unchanged drug are found in the urine (PDR, 1997).

Ticlid is recommended to be taken with food to maximize its gastrointestinal tolerance. There is 20% increase in oral bioavailability of ticlopidine when taken after a meal (PDR, 1997).

I. SINGLE-DOSE STUDY UNDER FASTING CONDITIONS:

Objective:

The purpose of this study was to compare the relative bioavailability of the test and reference ticlopidine

formulations when given after an overnight fast to healthy, adult, male subjects.

Methods
Study Design:

The clinical study was conducted at , under the supervision of , .

Forty-six male volunteers (44 and 2 alternates) between the ages of 18-45 years and within 20% of ideal body weight were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry, urinalysis, HIV-AIDS test, hepatitis B surface antigen, and urine drug screen].

Those with any of the following conditions were excluded:

History or presence of significant:

- cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.

History or presence of:

- hypersensitivity or idiosyncratic reaction to ticlopidine HCl
- alcohol or drug abuse

Rx and OTC medications (excluding vitamins) were not allowed within 7 days of the first drug administration. There was to be no alcohol or caffeine consumption at least 24 hours prior to drug administration and throughout the sample collection period.

The study was designed as a randomized, open-label, two-way crossover study with a 14 day washout period between dosing. Treatments consisted of a single 250 mg dose of the following:

A. Ticlopidine HCl, 250 mg tablet.

Eon Pharm Inc.
Batch #970605, batch size: tablets, content uniformity: 98.7% - 101.4%, potency: 99.0%
Expiry date: not given

B. Ticlid®, 250 mg tablet.
Syntex Laboratories Inc.
Batch #07609A, content uniformity: 100% - 103.6%, potency: 100.5%
Expiry date: October, 1998

Forty-six subjects were dosed according to the following randomization schedule:

AB: 1, 2, 3, 5, 9, 10, 11, 15, 16, 17, 19, 21, 22, 27, 28 31, 33, 34, 36, 37, 39, 40, 45
BA: 4, 6, 7, 8, 12, 13, 14, 18, 20, 23, 24, 25, 26, 29, 30 32, 35, 38, 41, 42, 43, 44, 46

Study Dates:
Period I: July 26,1997
Period II: August 9,1997

After an overnight fast, subjects were given a 250 mg dose of ticlopidine with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers containing EDTA at 0 (pre-dose, 2 x 10 ml), 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours. Subjects were released after the 36-hour blood draw and returned to the clinical facility for their subsequent blood draws. Following collection, the blood samples were centrifuged and stored frozen at -20° C until analysis.

ANALYTICAL METHODOLOGY

The plasma samples were assayed for ticlopidine by a method (using developed by . Sample preparation consisted of The resulting solution was then Quantitation of drug levels was based on of ticlopidine to internal standard vs standard concentration, using a

linear least squares fit weighted by 1/conc.
Sample analysis was conducted between August 15, 1997 and September 30, 1997.

PHARMACOKINETIC Methods: Pharmacokinetic parameters (areas, times to peak, elimination rates and half-lives) were calculated. Peak concentration (Cmax) was the observed maximum value. The time to peak concentration (Tmax) was the time at which Cmax was observed. The apparent first-order elimination rate (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. Elimination half-life (ELIMHALF) was calculated as 0.693/Ke.
Area under the curve (AUC) to the time of the last non-zero concentration was calculated by the linear trapezoidal method. Area to infinite time (AUCinf) was calculated by extrapolating AUC by the addition of the quantity: C_{last}/Ke.

STATISTICAL ANALYSES

Statistical analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program. Hypothesis testing for treatment effects was conducted at alpha= 0.05. The statistical model contained main effects of sequence, subject within sequence, period, and treatment. Sequence effects were tested against the type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term.
The observed and calculated pharmacokinetic parameters were compared statistically.
Confidence Intervals (90%) for pair-wise area and peak concentration comparisons were calculated by the t-test approach (2,1-sided) at alpha=0.10 overall, alpha=0.05 each side.

RESULTS

Pre-Study Assay Validation

Assay sensitivity: The limit of sensitivity of the assay was defined as ıL, with values less than this reported as zero.

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Subject Completion:

A total of 46 subjects were entered into the study and all subjects completed the study. As indicated in the protocol, statistical analyses were performed on the first 44 subjects completing the study (subject #1 to 44).
Mean plasma concentrations for Ticlopidine 250 mg in 44 subjects are shown in the table below:

	TEST		REFERENCE	
	MEAN	%CV	MEAN	%CV
HOUR0	0.00	0.00	0.00	0.00
HOUR0.5	22.09	214	11.73	144.8
HOUR1	226.54	101	190.80	89.1
HOUR1.3	372.51	75.5	322.20	62.5

HOUR1.67	471.70	55.9	440.07	53.5
HOUR2	485.18	49.3	490.99	49.9
HOUR2.3	451.82	50.7	472.15	54.0
HOUR2.67	366.28	59.0	384.11	53.8
HOUR3	306.75	70.5	329.57	61.1
HOUR3.5	211.39	70.6	228.69	73.5
HOUR4	155.45	68.5	169.79	78.6
HOUR6	52.14	54.2	54.36	60.9
HOUR8	34.97	53.8	36.52	64.1
HOUR12	21.07	52.1	21.75	61.7
HOUR16	14.53	56.0	14.77	54.4
HOUR24	9.30	50.4	9.14	49.8
HOUR36	5.17	71.6	4.88	68.5
HOUR48	3.32	80.6	3.10	83.2
HOUR72	1.54	117.7	1.32	136.5

The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, half-life, and elimination rate constant.

It is noted that:

The Sponsor reported that there were 12 cases where predose levels were detected in 12 subjects as follows: For the test treatment: Subject # 6, 18, 25, 32, 41, and 42, and for the reference treatment: Subject # 10, 16, 17, 19,21 and 36. All events occurred in the second period and the detected levels were below the LOQ, suggesting a possibility of an inadequate washout between study period.

There was no Cmax at the first non zero concentration, in any subject.
From plasma concentration-time profiles submitted, irregularity (V-shaped or inverted V-shaped) was observed at the terminal elimination phase of the following six (6) subjects (Subject #1, 8, 19, 21, 32, and 33). Kel was therefore, estimable for 38 subjects in this study.
Area under the curve(0-t) and AUC(0-inf) were calculated as well as elimination parameters for each subject. Observed values for Tmax and Cmax were also reported.

Mean pharmacokinetic parameters for subjects that received the test and reference ticlopidine formulations following an

Figure 1

Project No. 962024

Mean Plasma Ticlopidine Concentrations

(Semi – Log Plot)

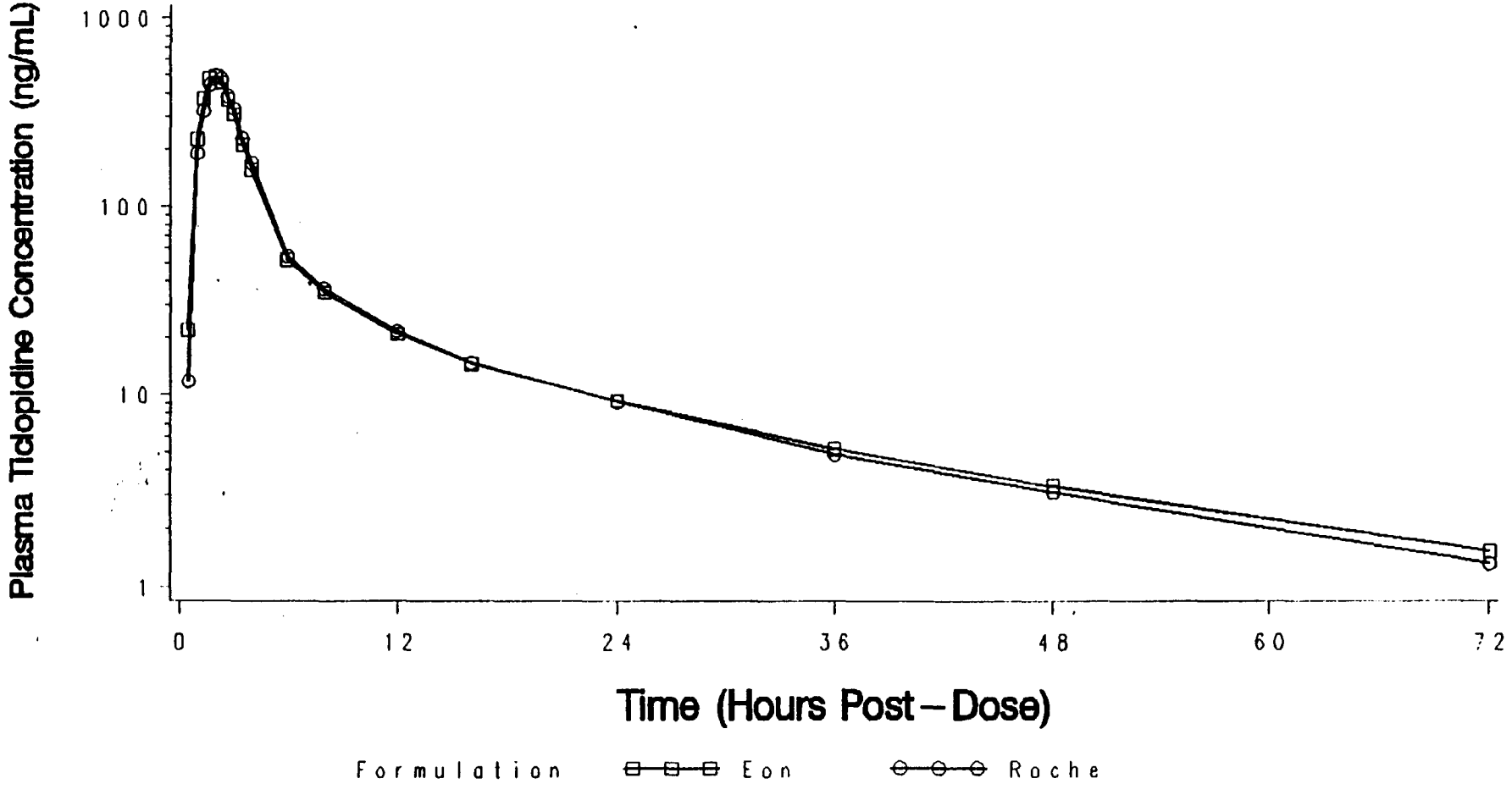
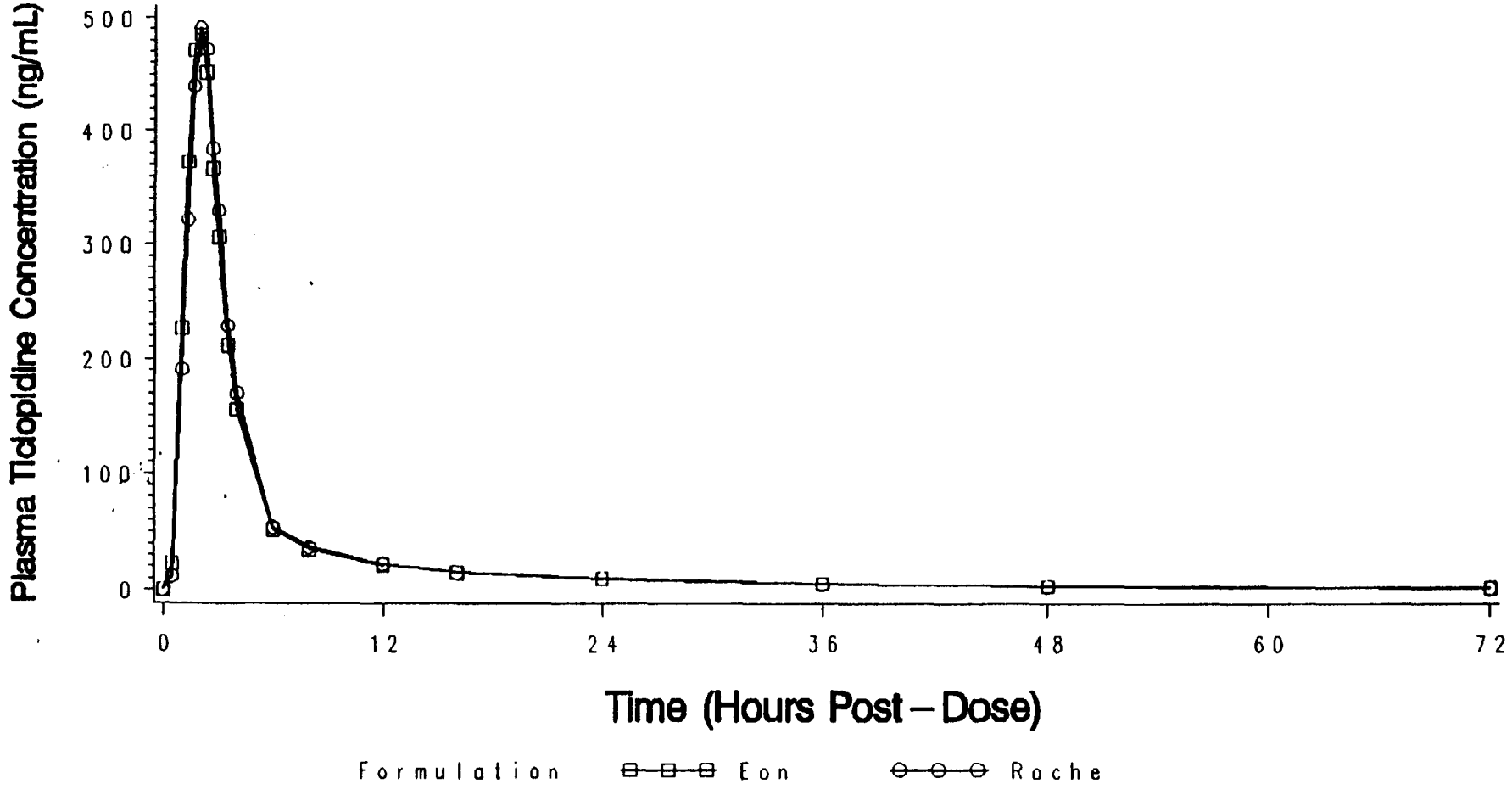


Figure 2

Project No. 962024

Mean Plasma Ticlopidine Concentrations

(Linear Plot)



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overnight fast are reported by the Sponsor as shown below:

	TREATMENT			
Variable	A=TEST (%CV)	B=REFERENCE (%CV)	Ratio (A/B)	N
AUC ng/mlxhr	1849.1 (50.8)	1850.4 (49.5)	0.99	44
AUCI ng/mlxhr	1928.7 (50.2)	1921.8 (49.7)	1.0	43
CPEAK (ng/ml)	609.10 (46.2)	599.86 (42.1)	1.01	44
KEL (1/hr)	0.046 (20.5)	0.049 (35.9)	0.94	43
HALF-Life (hr)	17.09 (33.8)	15.80 (31.6)	1.08	43
TPEAK (hr)	2.02 (24.7)	1.99 (23.7)	1.01	44

The pharmacokinetic parameters and drug plasma concentrations were evaluated statistically by ANOVA for differences due to treatments, study days, dosing sequence, and subjects within sequence. The statistical analysis was performed using SAS software. The SAS GLM procedure was used for the analysis of variance. The study power calculations and 90% confidence interval calculations were based on the least-squares means values generated by the SAS LSMEANS option to the SAS GLM procedure and the standard error of the estimate as given by the GLM procedure.

90% C.I limits on log transformed parameters below were reported by the Sponsor:

LAUCt: 92.1% - 104.6%
LAUCinf: 91.7% - 103.6%
LCmax: 91.3% - 105.3%

ALL CALCULATIONS WERE NOT VERIFIED BY THE REVIEWER AT THIS TIME DUE TO DEFICIENCIES CITED IN THE DEFICIENCY SECTION. FURTHERMORE, DATA PROVIDED BY THE FIRM IN THE DISKETTE WAS INCOMPLETE (only data of 15 subjects were provided).

Adverse Events:

No serious adverse events were reported in this study. A summary of all reported adverse events have been tabulated and can be found in the Appendix at the end of the review. They were evenly distributed between test and reference treatments.

II. SINGLE-DOSE STUDY UNDER FED CONDITIONS:

Objective:

The purpose of this study was to compare the relative bioavailability of the test and reference ticlopidine formulations under post-prandial and fasting conditions in healthy, adult, male subjects.

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The inclusion and exclusion criteria for subject selection were also the same.

The study was a randomized, three treatment, three period, six sequence crossover. Treatments consisted of the same two batches/lots of test and reference products (used in the fasting study). A 14 day washout period separated the dosing.

Twenty one (21) subjects were dosed according to the following regimen:

sequence	subject #
ABC	5, 6, 10, 19
ACB	2, 7, 11, 21
BAC	13, 16, 18
BCA	3, 8, 14
CAB	4, 9, 12, 20
CBA	1, 15, 17

Treatment A: 1 x 250 mg ticlopidine HCl tablet (Eon Pharm) following an overnight fast.
Treatment B: 1 x 250 mg ticlopidine HCl tablet (Eon Pharm) following a standard breakfast.
Treatment C: 1 x 250 mg Ticlid® tablet (Syntex) following a standard breakfast as follows:

1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk

After an overnight fast, subjects on treatment B or C were served a standard breakfast 30 minutes before dosing (entire meal to be consumed in 30 minutes). Fasting continued for 4 hours post dose. The sampling schedule protocol followed that used in the fasting study.

Results:

Assay Validation

Same as for fasting study.

Subject Completion:

21 subjects enrolled in and all completed the study. As per protocol, only data from first 18 subjects were used (subject #1-18).

Statistical Methods:

Same as for fasting study.

Pharmacokinetic Methods:

Same as for fasting study.

RESULTS

Mean plasma concentrations ng/ml$\pm$ SD for subjects that received the test and reference Ticlopidine 250 mg tablets under fed and fasting conditions. 21 subjects were dosed in periods I, II and III. The data presented is for the 18 subjects whose data were analyzed as specified in the protocol.

	TEST (Fast)		TEST (Fed)		REFERENCE (Fed)	
	MEAN	%CV	MEAN	%CV	MEAN	%CV
HOUR0	0	0	0	0	1.37	424.3
HOUR0.5	27.16	172.2	5.40	175.2	17.24	238.6
HOUR1	257.13	84.8	166.47	151.5	262.47	148.0
HOUR1.3	441.05	66.2	354.56	99.2	369.72	106.5
HOUR1.67	585.05	48.6	498.30	62.0	444.73	62.8
HOUR2	661.78	34.7	559.35	42.8	478.23	46.0
HOUR2.3	594.49	34.1	541.69	28.7	450.66	36.0
HOUR2.67	480.66	43.6	511.22	33.6	450.33	41.5
HOUR3	386.09	41.1	453.74	45.5	403.03	45.5
HOUR3.5	254.66	38.6	353.41	45.8	310.62	45.2
HOUR4	188.16	41.5	263.89	47.4	236.20	44.1
HOUR6	73.75	37.1	92.30	38.1	86.51	41.4
HOUR8	48.93	41.2	51.20	35.7	45.41	40.1
HOUR12	28.55	40.3	30.93	34.1	29.61	32.9
HOUR16	20.69	36.2	22.08	37.4	21.17	37.6
HOUR24	13.57	37.7	15.06	40.6	14.24	39.0
HOUR36	8.12	41.5	9.30	39.8	8.66	34.4
HOUR48	5.27	41.2	6.24	43.3	8.77	125.4
HOUR72	3.41	90.4	6.20	173.7	5.17	160.8

The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, half-life, and elimination rate constant.

<u>It is noted that</u>:

The Sponsor reported that, there were 21 cases where predose levels were detected in 14 subjects as follows: Subject # 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, and 18. All of the events occurred in the second or third period, and most of the detected levels were below the LOQ, suggesting a possibility of an inadequate washout between study periods.

There was no Cmax at the first non zero concentration, in any subject.

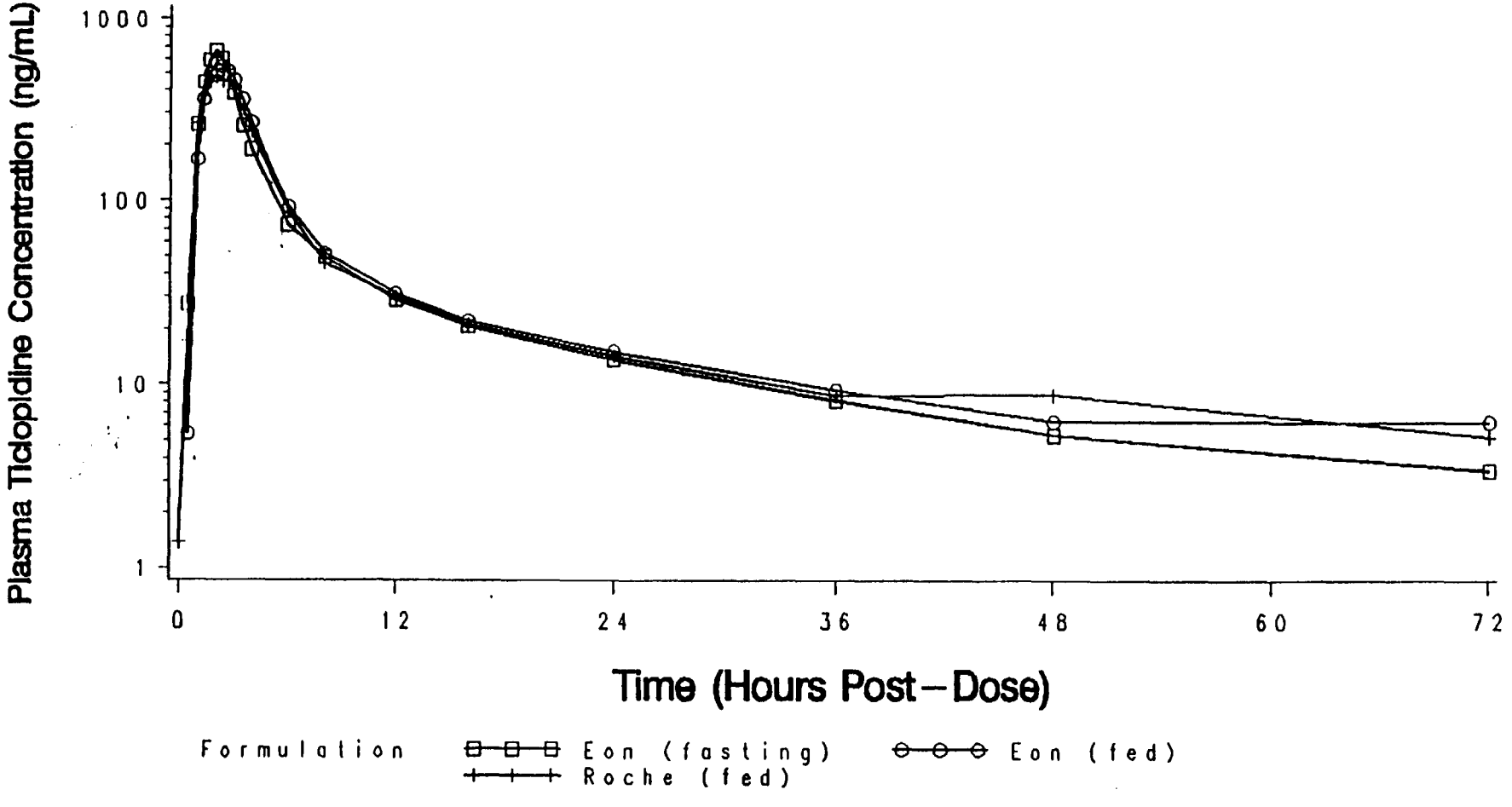
From plasma concentration-time profiles submitted, irregularity (V-shaped or inverted V-shaped) was observed at the terminal elimination phase of the following 3 subjects (Subject #8, 10, and 12). Kel was estimable for 15 subjects in this study. Area under the curve(0-t) and AUC(0-inf) were calculated as well as elimination parameters. Observed values for Tmax and Cmax were also reported.

Figure 1

Project No. 962025

Mean Plasma Ticlopidine Concentrations

(Semi – Log Plot)



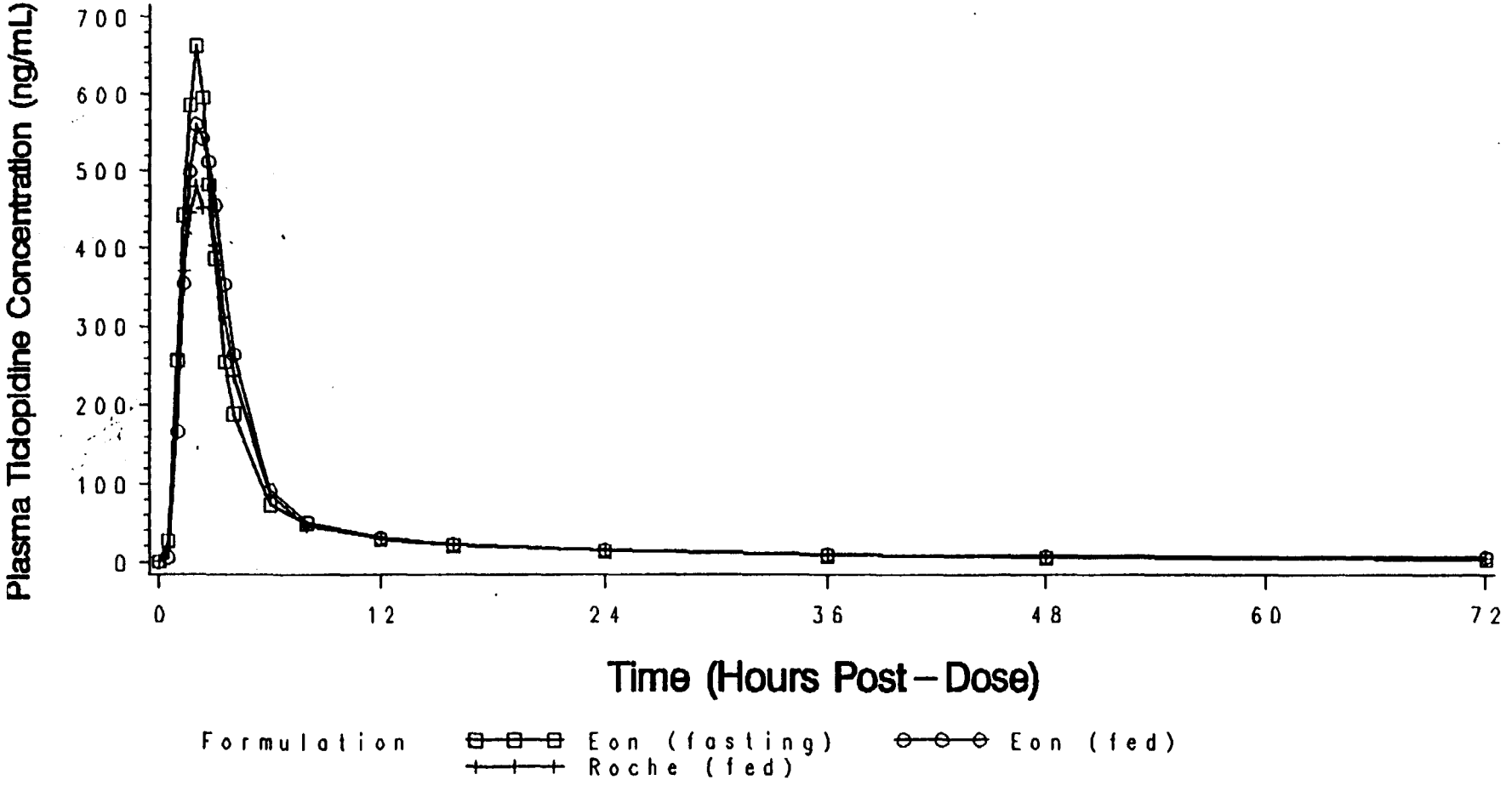
4371

Figure 2

Project No. 962025

Mean Plasma Ticlopidine Concentrations

(Linear Plot)



4372

Mean pharmacokinetic parameters for subjects that received the test and reference ticlopidine formulations following an overnight fast or after a standard breakfast are reported by the Sponsor as shown below:

Variable	Test-Fast	Test-Fed	Ref.-Fed	Fed T/R
AUCL ng/mLxhr	2471.7 (34.9)	2616.7 (31.0)	2507.5 (29.0)	1.04
AUCI ng/mLxhr	2597.1 (35.5)	2659.1 (32.9)	2598.5 (30.6)	1.02
Cmax ng/mL	727.38 (33.8)	712.50 (28.7)	730.68 (41.3)	0.97
KEL (hr-1)	0.033 (30.6)	0.032 (26.9)	0.032 (23.6)	1.0
HALF-LIFE (hr)	22.75 (32.6)	23.01 (25.0)	22.51 (17.9)	1.02
TMAX (hr)	1.98 (20.0)	2.20 (26.0)	2.06 (37.9)	1.07

Summary of Least-Squares Means Bioavailability Parameters along with calculated ratios of the Test(fed)/Ref(fed) for Ticlopidine. Parameters as reported by the Sponsor.

Variable	Test-Fast	Test-Fed	Ref.-Fed	T-Fed/R-Fed
AUCL	2284.32	2400.37	2470.96	0.97
AUCI	2402.82	2453.45	2470.96	0.95
Cmax	671.55	647.41	722.21	0.89

ALL CALCULATIONS WERE NOT VERIFIED BY THE REVIEWER AT THIS TIME BECAUSE THE DISKETTE PROVIDED BY THE FIRM WAS DEFECTIVE.

Adverse Events:

A summary of all reported adverse events have been tabulated and can be found in the Appendix Section at the end of the review for information.

Dissolution

The dissolution study for Ticlopidine HCL tablets was conducted by the Sponsor. This was not an official USP method, but it was the same as the FDA method except that the FDA specification is

Table 6. In Vitro Dissolution Testing---Not an official USP method.

Drug (Generic Name):Ticlopidine HCL
ANDA No.:75-326
Submission Date: January 30, 1998
File Name: 75326SD.198

Dose Strengths: 250 mg
Firm: Eon Laboratories

I. Conditions for Dissolution Testing:

USP XXIII, Paddle, RPM: 50
Medium: Water
Specifications:
Assay Methodology:

No. Units Tested: 12
Volume: 900 mL
Reference Drug: Ticlid -Roche

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 970605 Strength(mg) 250			Reference Product Lot # 07609A Strength(mg) 250		
	Mean	Range	%CV	Mean	Range	%CV
10	79.6	[illegible]	8.7	89.4	[illegible]	6.7
20	86.7	[illegible]	5.0	93.4	[illegible]	5.1
30	89.6	[illegible]	4.0	95.6	[illegible]	4.4
45	92.1	[illegible]	3.5	97.0	[illegible]	3.4
60	93.6	[illegible]	3.0	97.8	[illegible]	2.8

FORMULATION:

The formulation for the test product was as follows:

Ingredient	Amount/Tablet, mg
CORE TABLET	
Ticlopidine	
Micro. Cellulose	[redacted]
Micro. Cellulose	
Povidone	
Starch	
Colloidal Silicon Dioxide	
Magnesium Stearate	
Purified Water	
TOTAL CORE TABLET WEIGHT	
COAT	

Deficiencies:

1. For the fasting and non fasting studies, it is requested to use the last three or four data points in computing Kel for appropriate estimation of the elimination rate constants, and hence AUCinf. New data should be generated and submitted along with appropriate statistical results for evaluation.

2. For both studies, subjects with irregularities at the terminal phase of the plasma concentration-time plots (V-shaped or inverted V-shaped) should be deleted from statistical analysis of AUCinf. New data should be generated and submitted along with appropriate statistical results.

3. For both studies, the subjects who had levels above the LOQ at time zero, should be deleted from all analyses. New data should be generated and submitted to the Agency for evaluation.

4. Detected levels, although below LOQ, were seen in many subjects in both studies **(fasting study, 12 subjects: # 6, 18, 25, 32, 41, 42, 10, 16, 17, 19, 21 and 36, and fed study, 14 subjects: # 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, and 18)**, and in addition, all events occurred in the second (fasting) or second and/or third (fed) period suggesting an incomplete washout

time between periods. Is the observed phenomenon in violation of the basic statistical assumption of a cross-over design? Complete documentation should be provided to explain the observed phenomenon.

5. Please submit all requested information in an electronic format (SAS or ASCII format) along with a hard copy for evaluation. Please make sure that the diskette is not defective and contains complete data as requested.

Recommendation

1.The fasting and nonfasting bioequivalence studies conducted by Eon on its 250 mg Ticlopidine Tablets, lots #970605 comparing them to Roche's Ticlid[R] 250 mg tablets have been found incomplete by the Division of Bioequivalence.

2.The in vitro dissolution testing conducted on the 250 mg strength (lot # #970605), is acknowledged.

/S/

Nhan L. Tran, Ph.D.

Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR /S/ Date: 7/2/1998
FT INITIALED SNERURKAR

Concur /S/ Date: 7/6/98

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

IFD-

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA:75-326 APPLICANT: Eon Laboratories
DRUG PRODUCT: Ticlopidine HCL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. For the fasting and non fasting studies, it is requested to use the last three or four data points in computing Kel for appropriate estimation of the elimination rate constants, and hence AUCinf. New data should be generated and submitted along with appropriate statistical results for evaluation.

2. For both studies, subjects with irregularities at the terminal phase of the plasma concentration-time plots (V-shaped or inverted V-shaped) should be deleted from statistical analysis of AUCinf. New data should be generated and submitted along with appropriate statistical results.

3. For both studies, the subjects who had levels above the LOQ at time zero, should be deleted from all analyses. New data should be generated and submitted for evaluation.

4. Detected levels, although below the LOQ, were seen in many subjects in both studies **(fasting study, 12 subjects: # 6, 18, 25, 32, 41, 42, 10, 16, 17, 19, 21 and 36, and fed study, 14 subjects: # 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, and 18)**, and in addition, all events occurred in the second (fasting) or second and third (fed) period suggesting an incomplete washout time between period. Is the observed phenomenon in violation of the basic statistical assumption of a cross-over design? Please explain.

5. Please submit all requested information in electronic format (SAS or ASCII format) along with a hard copy for evaluation. Please make sure that the diskette is not defective and contains complete data as requested.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs, CDER.

CC:

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Endorsements: (Final with Dates)
HFD-655 Reviewer
HFD-655/ Bio team Leader 7/2/98
HFD-650/ D. Conne 6/16/98

BIOEQUIVALENCY - DEFICIENCIES Submission Date: Jan 30, 1998

1. **FASTING STUDY** (STF) Strengths: 250 mg
   Clinical: F **Outcome: IC**
   Analytical

2. **FOOD STUDY** (STP) Strengths: 250 mg
   Clinical: F **Outcome: IC**
   Analytical:

3. ~~**DISSOLUTION DATA**~~ (DIS) All Strengths
   Outcome: NC

Outcome Decisions: Fasting Study **IC** - Incomplete
Non-fasting study **IC** - Incomplete

(Fast)

TABLE C1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject	Product Code Period 1	2	Age (yrs)	Height (cm)	Weight (kg)	Frame	Gender	Race
1	A	B				Medium	Male	Caucasian
2	A	B				Medium	Male	Caucasian
3	A	B				Medium	Male	Caucasian
4	B	A				Medium	Male	Caucasian
5	A	B				Medium	Male	Caucasian
6	B	A				Medium	Male	Caucasian
7	B	A				Small	Male	Caucasian
8	B	A				Medium	Male	Caucasian
9	A	B				Medium	Male	Caucasian
10	A	B				Medium	Male	Caucasian
11	A	B				Medium	Male	Caucasian
12	B	A				Medium	Male	Caucasian
13	B	A				Small	Male	Caucasian
14	B	A				Small	Male	Caucasian
15	A	B				Medium	Male	Caucasian
16	A	B				Small	Male	Caucasian
17	A	B				Medium	Male	Caucasian
18	B	A				Small	Male	Caucasian
19	A	B				Medium	Male	Caucasian
20	B	A				Medium	Male	Caucasian
21	A	B				Medium	Male	Caucasian
22	A	B				Medium	Male	Caucasian
23	B	A				Medium	Male	Caucasian
24	B	A				Medium	Male	Caucasian
25	B	A				Medium	Male	Caucasian
26	B	A				Medium	Male	Caucasian
27	A	B				Small	Male	Caucasian
28	A	B				Medium	Male	Caucasian
29	B	A				Small	Male	Caucasian
30	B	A				Medium	Male	Caucasian
31	A	B				Medium	Male	Caucasian
32	B	A				Medium	Male	Caucasian
33	A	B				Medium	Male	Caucasian
34	A	B				Medium	Male	Caucasian
35	B	A				Medium	Male	Caucasian
36	A	B				Medium	Male	Caucasian
37	A	B				Medium	Male	Caucasian
38	B	A				Medium	Male	Caucasian
39	A	B				Medium	Male	Caucasian
40	A	B				Medium	Male	Caucasian
41	B	A				Medium	Male	Caucasian
42	B	A				Small	Male	Caucasian
43	B	A				Medium	Male	Caucasian
44	B	A				Medium	Male	Caucasian
45	A	B				Small	Male	Caucasian

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

Subject ages are calculated as of Period 1 dosing.

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-F10-R10

TABLE C1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject	Product Code Period 1 2	Age (yrs)	Height (cm)	Weight (kg)	Frame	Gender	Race
46	B A				Medium	Male	Caucasian
	Mean	28.5	174.6	71.56			
	± SD	7.03	5.73	6.553			
	N	46	46	46			
	CV%	24.7	3.3	9.2			

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

Subject ages are calculated as of Period 1 dosing.

File DEMO.OUT created 03/OCT/97 02:25pm by JOBIND01. DataBase Ver# 4.53, Internal Ver# 97.01
-F10-R10

TABLE C3
Medical Events Summary

TOTAL PRE-DOSE EVENTS = 0

POST-DOSE: RELATED TO THE STUDY DRUG

PROBABLY = 2

Product Code A
Feels nauseous (2)
Product Code B
None

POSSIBLY = 5

Product Code A
Loose stools (1)
Product Code B
Dizzy (1)
Loose stool (liquid) (1)
Loose stools (1)
Nauseous (1)

UNLIKELY = 2

Product Code A
None
Product Code B
Headache (2)

POST-DOSE: RELATED TO SOMETHING OTHER THAN THE STUDY DRUG OR THE STUDY PROCEDURES

DEFINITELY = 1

Product Code A
None
Product Code B
Sore left foot due to car driving over it (1)

PROBABLY = 1

Product Code A
None
Product Code B
Redness on penis (1)

POSSIBLY = 3

Product Code A
Headache (1)
Product Code B
Headache (1)
Lower left abdominal region: burning sensation (1)

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

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TABLE C3
Medical Events Summary (Cont'd)

POST-DOSE: RELATED TO THE STUDY PROCEDURE (S)

DEFINITELY = 1

Product Code A
Bleeding at venipuncture site (1)
Product Code B
None

TOTAL POST-DOSE EVENTS = 15

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

S:\CLIN\REPS\96\962024.MES

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu-tion	Inten-sity	Action/Comment
Product Code A														
13	2	08:24am 09/AUG/97	**Feels nauseous**											
			38.0m	1.1h	NS	D	PR	SP	M	None	1.7h	R	N/A	None
37	1	09:12am 26/JUL/97	**Loose stools**											
			33.0m	2.3h	NS	D	PO	SP	M	None	2.8h	R	N/A	None
46	2	09:30am 09/AUG/97	**Feels nauseous**											
			45.0m	1.8h	NS	D	PR	SP	M	None	1.7h	D	M	None
											2.5h	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

2126

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

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TABLE C4

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious -ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used		Follow-Up Time after dosing	Evolu -tion	Inten -sity	Action/Comment
Product Code B															
6	1	08:10am 26/JUL/97	**Headache**												
			50.0m	11.2h	NS	D	U	SP	M	None		12.0h	R	N/A	None
37	2	09:12am 09/AUG/97	**Loose stools** (liquid)												
			1.1h	1.2h	NS	D	PO	SP	M	None		*	N/A	N/A	Had three episodes of loose stools between onset and time of reporting *Date/time of comment not recorded
												2.3h	R	N/A	None
46	1	09:30am 26/JUL/97	**Dizzy**												
			30.0m	1.5h	NS	D	PO	SP	M	PO		1.1h	I	M	B.P.: 108/62 (semi-reclined), pulse: 76
												2.0h	R	N/A	None
46	1	09:30am 26/JUL/97	**Nauseous**												
			30.0m	45.0m	NS	D	PO	SP	M	PO		1.2h	I	M	Applied cold compress on forehead and back of neck 1.1h post-dose
												1.3h	R	N/A	None
46	1	09:30am 26/JUL/97	**Headache**												
			1.3h	55.0m	NS	D	U	E	M	PO	MP	1.8h	I	M	2 x 500 mg acetaminophen caplets given at 2.0 h post-dose
												2.2h	R	N/A	None
46	1	09:30am 26/JUL/97	**Loose stool**												
			1.9d	4.5d	NS	D	PO	E	MO	None		6.4d	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet

Statistical Analyses (cont'd)

The following formulae were used for the ratio of means, confidence interval, power and intrasubject variability calculations:

	Untransformed Parameters	Log-Transformed Parameters
Ratio of Means:	$100 * (\frac{LSM_t}{LSM_r})$	$100 * e^{(LSM_t - LSM_r)}$
90% Confidence Interval:	$100 * (\frac{LSM_t \pm t_{df,0.05} * SE_{t-r}}{LSM_r})$	$100 * e^{(LSM_t - LSM_r \pm t_{df,0.05} * SE_{t-r})}$
Power:	$100 * Prob\left(\frac{0.2 LSM_r}{SE_{t-r}} - t_{df,0.025} > t_{df}\right)$	$100 * Prob\left(\frac{\ln(1.25)}{SE_{t-r}} - t_{df,0.025} > t_{df}\right)$
Intrasubject CV%:	$100 * \frac{\sqrt{MSE}}{OVERALL\ MEAN}$	$100 * \sqrt{e^{MSE} - 1}$

Note: $t_{df,\alpha}$ is the value of the Student's t-distribution with df degrees of freedom (ie. degrees of freedom for the error term from the analysis of variance) and a right-tail fractional area of α.

LSM is the least-squares mean of the test or reference formulation, as computed by the LSMEANS statement of the SAS® GLM procedure.

MSE is the mean square error from the analysis of variance.

Overall Mean is the combined mean value for each parameter, as calculated by the SAS® GLM procedure.

SE_{t-r} is the standard error of the adjusted difference between the formulation means, as computed by the ESTIMATE statement in the SAS® GLM procedure. For a balanced study, SE_{t-r} is equal to the square root of 2*MSE/n, where n is the number of subjects.

Period Effect

A statistically significant period effect ($p < 0.05$) was observed for log-transformed AUCinf and Cmax parameters. Given that period and treatment effects are orthogonal in a balanced, randomized crossover design, period differences do not affect the bioequivalence assessment.

Reference

1. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 1987;15 657-80.

Fed

TABLE C1

SUBJECT DEMOGRAPHICS AND RANDOMIZATION SCHEME

Subject	Regimen Period 1 2 3	Age (yrs)	Height (cm)	Weight (kg)	Frame	Gender	Race
1	C B A				Medium	Male	Caucasian
2	A C B				Medium	Male	Caucasian
3	B C A				Medium	Male	Caucasian
4	C A B				Medium	Male	Caucasian
5	A B C				Medium	Male	Caucasian
6	A B C				Small	Male	Caucasian
7	A C B				Medium	Male	Caucasian
8	B C A				Medium	Male	Caucasian
9	C A B				Medium	Male	Caucasian
10	A B C				Small	Male	Caucasian
11	A C B				Small	Male	Caucasian
12	C A B				Medium	Male	Caucasian
13	B A C				Medium	Male	Caucasian
14	B C A				Small	Male	Caucasian
15	C B A				Medium	Male	Caucasian
16	B A C				Medium	Male	Caucasian
17	C B A				Small	Male	Caucasian
18	B A C				Medium	Male	Caucasian
19	A B C				Small	Male	Caucasian
20	C A B				Small	Male	Caucasian
21	A C B				Medium	Male	Caucasian
Mean		28.1	174.3	74.51			
± SD		6.04	4.93	6.266			
N		21	21	21			
CV%		21.4	2.8	8.4			

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

Subject ages are calculated as of Period 1 dosing.

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TABLE C3

Medical Events Summary

PRE-DOSE EVENTS:

*Nausea (Subject No. 12)
*Bruise at venipuncture site (right arm) (Subject No. 15)

*The Medical Designate could not address the subject's eligibility for Period 1 dosing as these events were reported after dosing.

TOTAL PRE-DOSE EVENTS = 2

POST-DOSE EVENTS: RELATED TO THE STUDY DRUG 11

PROBABLY = 2

Regimen A
Loose stool (1)
Nausea (1)
Regimen B
None
Regimen C
None

POSSIBLY = 2

Regimen A
Bleeding gums (1)
Flatulence (1)
Regimen B
None
Regimen C
None

UNLIKELY = 7

Regimen A
None
Regimen B
Feels tired (1)
Headache (1)
Pimples on his face (1)
Rash on lips (1)
Regimen C
Headache (2)
Pimples on his face (1)

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

S:/CLIN/REPS/96/962025.MES

TABLE C3

Medical Events Summary (Cont'd)

RELATED TO SOMETHING OTHER THAN THE STUDY DRUG OR STUDY PROCEDURES 14

DEFINITELY = 4

Regimen A
Headache (1)
Regimen B
Headache (1)
Regimen C
Feels feverish (1)
Sore throat (1)

PROBABLY = 10

Regimen A
Blocked nasal passage (1)
Feels fever (1)
Sore throat (1)
Regimen B
Blocked nose (1)
Sore throat (1)
Regimen C
Coughing (1)
Chest congestion (1)
Headache (1)
Loss of voice (1)
Nose is blocked (1)

RELATED TO THE STUDY PROCEDURES 2

PROBABLY = 2

Regimen A
Feels dizzy (1)
Nausea (1)
Regimen B
None
Regimen C
None

TOTAL POST-DOSE EVENTS = 26

A = Eon 1 x 250 mg ticlpidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

S:/CLIN/REPS/96/962025.MES

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom								Follow-Up			
			Time after dosing	Duration	Seriousness	Causality	Probability	Report Method	Intensity at Onset	Forms Used	Time after dosing	Evolution	Intensity	Action/Comment
Regimen A														
15	3	08:28am 01/NOV/97	**Loose stool**											
			3.8h	1.1d	NS	D	PR	SP	M	None	5.8h	U	M	None
											1.0d	D	M	None
											1.3d	R	N/A	None
15	3	08:28am 01/NOV/97	**Nausea**											
			5.7h	3.8h	NS	D	PR	SP	M	None	9.5h	R	N/A	None
17	3	08:32am 01/NOV/97	**Flatulence**											
			1.5h	2.3d	NS	D	PO	E	M	None	2.4d	R	N/A	None
17	3	08:32am 01/NOV/97	**Bleeding gums**											
			3.5h	*	NS	D	PO	E	M	None	3.0d	D	M	None
						* Duration: approximately 3 days					*	N/A	N/A	*Event lost to follow-up at approximately 25 days post-dose. Medical Designate will try to reach subject again soon
											*	R	N/A	None *Event resolved approximately 3.0 days post-dose (exact time of resolution unknown)

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

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TABLE C4

MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious -ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu -tion	Inten -sity	Action/Comment
Regimen B														
8	1	08:14am 04/OCT/97	**Headache**											
			1.1d	8.2h	NS	D	U	SP	M	None	1.2d	U	M	None
											1.4d	R	N/A	None
11	3	08:20am 01/NOV/97	**Feels tired**											
			1.0m	7.7h	NS	D	U	SP	M	None	32.0m	I	M	None
											7.7h	R	N/A	None
15	2	08:28am 18/OCT/97	**Pimples on his face**											
			3.5h	15.8d	NS	D	U	SP	M	None	1.5d	U	M	None
											1.5d	U	M	None
											2.0d	D	M	None
											3.0d	U	M	None
											13.4d	D	M	None
											14.0d	D	M	None
											15.5d	D	M	None
											15.9d	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

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MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious -ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu -tion	Inten -sity	Action/Comment
Regimen B														
15	2	08:28am 18/OCT/97	**Rash on lips**											
			15.4h	3.8d	NS	D	U	SP	M	None	1.5d	I	M	Vaseline was applied
											1.5d	I	M	None
											2.0d	D	M	None
											3.0d	D	M	None
											4.4d	R	N/A	None

TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other-MD's Comment	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

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MEDICAL EVENTS

Subj	Per	Dosing Time/ Date	Sign/Symptom Time after dosing	Dur-ation	Serious-ness	Caus-ality	Proba-bility	Report Method	Intensity at Onset	Forms Used	Follow-Up Time after dosing	Evolu-tion	Inten-sity	Action/Comment
Regimen C														
14	2	08:26am 18/OCT/97	**Headache**											
			1.3d	5.5h	NS	D	U	SP	M	None	1.6d	R	N/A	None
15	1	08:28am 04/OCT/97	**Pimples on his face**											
			3.5h	4.1d	NS	D	U	SP	M	None	4.2d	R	N/A	None
21	2	08:40am 18/OCT/97	**Headache**											
			1.3d	9.0h	NS	D	U	E	M	None	1.6d	R	N/A	None

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TIME UNITS	FORMS USED	SERIOUSNESS	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	PO=Physician Obs	S=Serious	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	AC=Addit. Comment	NS=Non-Serious	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes	MP=Med.Prescrip.		O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 250 mg ticlopidine HCl tablet (fasting).
B = Eon 1 x 250 mg ticlopidine HCl tablet (fed).
C = Roche (Ticlid) 1 x 250 mg ticlopidine HCl tablet (fed).

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-326 APPLICANT: Eon Laboratories

DRUG PRODUCT: Ticlopidine HCL

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 37^0 C using U.S.P. Apparatus (II) at 50 rpm. The test product should meet the following specifications:

[redacted] in [redacted].

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