CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-253

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

APR 8 1998

ANDA: 75-253 APPLICANT: Purepac Pharmaceutical Co.

DRUG PRODUCT: Ticlopidine Hydrochloride Tablets, 250 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 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

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

ANDA/AADA # 75-253 SPONSOR: Purepac Pharmaceutical Co.

DRUG & DOSAGE FORM: Ticlopidine HCl Tablets

STRENGTH(S): 250 mg

TYPE OF STUDY: Single dose fasting and non-fasting studies

STUDY SITE:

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic and dissolution data of ticlopidine tablets. The firm has conducted single-dose fasting and nonfasting studies, and dissolution testing on test and reference products. The results of the studies indicate that Purepac's 250 mg tablets are bioequivalent to the reference product, Roche Laboratories' Ticlid® 250 mg tablets. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{inf}$, and LC_{max} are in the acceptable range of 80-125 for single-dose study. As required, under fed conditions, the test/reference ratios for PK parameters were within 0.8-1.2.

DISSOLUTION:

The test product 250 mg tablets meet the agency's dissolution specifications (non-USP Method). The amount of drug dissolved from the test product was NI in 45 minutes.

PRIMARY REVIEWER: S.P.Shrivastava, Ph.D. BRANCH: II

INITIAL: _____ DATE 4/7/98

BRANCH CHIEF: S. G. Nerurkar, Ph.D. BRANCH: II

INITIAL _____ DATE 4/7/1998

DIRECTOR

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

INITIAL: _____ DATE 4/8/98

DIRECTOR

OFFICE OF GENERIC DRUGS: Douglas L. Sporn

INITIAL: _____ DATE _____

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0849

TELEPHONE AMENDMENT

UPS OVERNIGHT COURIER

April 16, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-253, TICLOPIDINE HYDROCHLORIDE TABLETS, 250 MG

Dear Mr. Sporn:

Reference is made to the April 15, 1998 telephone conversation between Ms. Kassandra Sherrod and Dr. Abraham Croitoru, of the Office of Generic Drugs, and Ms. Elizabeth Trowbridge, of Purepac, regarding Ticlopidine Hydrochloride Tablets, 250 mg, ANDA #75-253. In this conversation, Dr. Croitoru requested dissolution profiles performed on current room temperature stability samples utilizing the following conditions:

Medium:	900 mL WATER at 37°C
Apparatus:	2 (paddle) at 50 RPM

TELEPHONE AMENDMENT

TICLOPIDINE HYDROCHLORIDE TABLETS, 250 MG
ANDA #75-253

Accordingly, Purepac has conducted dissolution testing on twelve (12) units of test batch #PI-997, using the referenced conditions. The data presented was generated on samples from the nine (9) month test station of our ongoing room temperature stability study. Testing was performed on both our 30 unit and 100 unit packages. Presented with these profiles are the results of our initial dissolution testing, utilizing as the medium, and assay testing for the nine (9) month test station. Please refer to Section 1 of this submission for the requested information.

Furthermore, in accordance with recent information from the Division of Bioequivalence, Purepac commits to using the following dissolution conditions and tolerance for all future finished product release and stability testing:

Medium:	900 mL WATER at 37°C
Apparatus:	2 (paddle) at 50 RPM
Tolerance:	

In conjunction with this submission, Purepac is providing a copy of the Telephone Amendment to our local district office. The required Field Copy Certification is included in Section 2.

As instructed by Ms. Sherrod, this information is being submitted as a **Telephone Amendment** and is being sent by overnight mail.

Purepac trusts that the data submitted in this **Telephone Amendment** will be found complete and in order and looks forward to the issuance of a final approval for this application.

If you have any questions regarding this submission, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge/for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

Attachments

Ticlopidine hydrochloride 250 MG Tablets
ANDA #75-253
Reviewer: S.P. Shrivastava
WP #75253SD.N97

Purepac Pharmaceutical Co.
Morgantown, WV
Submitted:
November 14, 1997
April 6, 1998

REVIEW OF TWO BIOEQUIVALENCE STUDIES, AND DISSOLUTION DATA

I. OBJECTIVES

Review of Purepac's two *in vivo* bioequivalence studies comparing its 250 mg strength ticlopidine hydrochloride tablets to Syntex (Roche's) 250 mg strength Ticlid[R] tablets, under fasting and non-fasting conditions. Initially the firm had submitted *in vitro* dissolution in · nedium. However, on April 6, 1998, the firm submitted dissolution in water as an amendment.

II. BACKGROUND

Drug Substance: Ticlopidine is a platelet aggregation inhibitor which is indicated to reduce the risk of thrombic stroke in patients who have had a thrombic stroke or have experienced stroke precursors. The drug inhibits the fibrinogen binding of platelets to form blood clots. The exact mechanism of action, however, is unknown.

After oral administration of a single 250 mg dose, ticlopidine is rapidly absorbed, with peak plasma levels (C_{max}) reached in about 2 hours. Absorption is greater than 80%, and administration after meals results in a 20% increase in the extent of absorption (AUC). Ticlopidine HCL displays non-linear pharmacokinetics and the clearance decreases markedly on repeated dosing. The drug's elimination half-life ($T_{1/2}$) following single oral doses of 250 mg to healthy males has been reported as about 7-8 hours. The drug binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. This binding is non-saturable over a wide concentration range.

Ticlopidine is rapidly metabolized by the liver; only trace amounts of intact drug are found in the urine. Over twenty metabolites have been identified in the urine and plasma. The drug is inactive in vitro, so a metabolite of ticlopidine may be the active antithrombotic agent; however, the product labeling states that no such metabolite has been isolated. Clearance of ticlopidine decreases with age and steady-state trough values in elderly patients (mean age 70 years) were about twice those in young volunteers.

The drug is marketed as Ticlid[R] 250 mg tablets (Syntex). The recommended dosage is 250 mg twice a day given with food to increase gastric tolerance.

Correspondence with Firm Related to BE Studies: On October 27, 1995, the firm had submitted a protocol for review (P95-143), where a deficiency was cited (OGD letter, dated 2/5/96) - ".... The protocol states that ticlopidine has at least one active metabolite, but has made no provision to measure it. Before the study begins, please either modify the protocol to provide for measuring the

active metabolite, or provide a rationale as to why the metabolite should not be measured. In the latter case, Division approval of the protocol is required before starting the study." The firm responded to the deficiency (see letter, dated June 12, 1996), and wrote justifications against measuring metabolite, which was acceptable to the Division ((see OGD letter, dated 9/12/96).

III. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # 951337

This open label, randomized, single-dose, two-way crossover study was conducted with 48 healthy male volunteers in accordance with the protocol. Two subjects #16 and 31 withdrew from the study after period 1 dosing, and Subject # 24 was taken off the study after first dose due to medical reasons. Thus 45 subjects completed the study. In each period, subjects received a single 250 mg dose of either Purepac's ticlopidine hydrochloride tablets or Syntex's Ticlid^{R} tablets following an overnight fast. There was a 14-day wash-out period between treatments. Blood samples were collected pre-dose and for 96 hours after each dose. Plasma concentrations of ticlopidine hydrochloride was measured by a fully validated procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference products.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two ticlopidine hydrochloride formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study.

4. Study sites — Clinical study:
Analytical study:

5. Study dates: June 12, 1997 - August 5, 1997

Clinical study:	6/12/97-6/30/97
Analytical study:	7/9/97-8/5/97
Storage Time:	54 Days

6. Investigators: Principal Investigators -

A. Reference: 250 mg Ticlid^{R} Tablets (Roche Labs., Lot #07635A);
Exp. Date 1/99; Potency - 98.4%.

B. Test: 250 mg Ticlopidine hydrochloride tablets (Purepac, Lot #PI-997); Rel. Date - 5/99; Lot Size otency -97.3 %.

Randomization Scheme: See Attachment-1.

7. Dosing: All doses were administered with of water. Subjects will fast for at least 10 hours pre- and 5 hours post-dosing.

8. Subjects: The 48 subjects who entered in this study were normal healthy male volunteers between the ages 18-45 years, and within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

   Forty-five subjects completed the study. Two subjects #16 and 31 withdrew from the study after period 1 dosing, and Subject # 24 was taken off the study after first dose due to medical reasons.

9. Food and fluid intake: Standard meals were served at 4 and 9 hours post-dose, and at appropriate times as scheduled on each day. The drug products were administered with mL of water. Water was allowed *ad lib.* except during one-hour pre- and two-hour, post-dosing periods.

10. Washout period: 14 Days between dose administration.

11. Blood samples: In each period, 10 mL of blood samples were collected in tubes containing EDTA at 0.0, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours. Plasma was separated and all plasma samples were stored frozen at -12°C until ready for analysis.

12. Subject safety monitoring: Subjects were asked to report any signs or symptoms that might be related to the drug products.

13. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.

14. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for ticlopidine hydrochloride. 90% confidence intervals were calculated for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max}.

B. Limited-Food Study

1. Protocol # 951336

2. Study design: Randomized, single-dose, three-way crossover, six sequence study under fasting/non-fasting conditions.

3. Study Sites and Investigators: Same as in the fasting study

4. Study dates: Clinical study: July 3, 1997-August 4, 1997
Analytical study: August 13, 1997-September 5, 1997
Total Storage Period: 64 Days

5. Treatments:

A. Test: 250 mg Ticlopidine hydrochloride Tablets (Purepac, Lot #PI-997, Exp. Date: 5/99, under fasting conditions.

B. Test: 1 X 250 mg Purepac ticlopidine hydrochloride tablets (Purepac, Lot #PI-997, Exp. Date: 5/99 under non-fasting conditions.

C. Reference: 1 X 250 mg Ticlid[R] tablet (Roche), Lot #07635A, Exp. Date 1/99) under non-fasting conditions.

Randomization Scheme: See Attachment-2.

6. Dosing: All doses were administered with mL of water at room temperature following an overnight fast or within 30 minutes of starting the breakfast depending on the dosing schedule.

7. Subjects: All 24 subjects entered and completed the study.

8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with of water. Water was allowed *ad lib.* except during two-hour pre-dose and two-hour post-dose periods.

9. Wash-out period: 14 Days between dosage administration.

10. Blood samples: Same as in the fasting study.

IV. PRE-STUDY VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.