ANDA 75-149 August 20,1999

Teva Pharmaceuticals, USA
Attention: Deborah A. Jaskot
1510 Delp Drive
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated June 20, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ticlopidine Hydrochloride Tablets, 250 mg.

Reference is also made to our tentative approval letter dated October 29, 1998, our approvable letter dated May 11, 1999, and to your amendments dated June 24, July 27, August 11, and August 16, 1999.

The listed drug product (RLD) referenced in your application, Ticlid Tablets of Syntex U.S.A. Inc., is subject to a period of patent protection which expires on May 27, 2003 (U.S. patent 4,591,592 [the '592 patent]. Your application contains a patent certification to the '592 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the Agency that Teva Pharmaceuticals USA, Inc. (Teva) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Teva within the statutory forty-five day period. However, the agency has been precluded from granting final approval to your application because of the eligibility for 180-day generic drug exclusivity granted to TorPharm, Inc. concurrently with the approval of their abbreviated application for Ticlopidine Hydrochloride Tablets, 250 mg, on July 1, 1999.

Further reference is made to litigation [Teva Pharmaceuticals

USA, Inc; Purepac Pharmaceutical Co.; and Invamed, Inc. v. United States Food and Drug Administration; TorPharm, a Division of Apotex, Inc.; and Hoffman-LaRoche, Inc. and Syntex (U.S.A.), Inc.] in the United States District Court for the District of Columbia, Civil Action No. 99-67 (CKK) in which the court entered a final judgement on August 18, 1999, in favor of the plaintiffs. This ruling effectively voided the agency's award of 180-day generic drug exclusivity to TorPharm, Inc. Additional reference is made to two unsuccessful appeals of this decision made by the defendants to both the district and appeals court level.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ticlopidine Hydrochloride Tablets, 250 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ticlid® Tablets, 250 mg of Syntex U.S.A., Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

We note that Teva has committed to provide a post-approval educational program that will be implemented upon the distribution and marketing of Ticlopidine Hydrochloride Tablets that incorporates the following elements:

1. Target audience for an adequate educational campaign.

    a. Physicians, including those within a health-care system such as an HMO or PPO, who prescribe Ticlopidine.

    b. Other health-care professionals, such as nurse practitioners, physician assistants, and dispensing pharmacists, who are in a position in a given health-care system to educate patients and/or monitor compliance.

2. Substantive elements of an adequate educational campaign.

    a. A clear statement that Ticlopidine is approved for use only in patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

    b. Discussion of the known risks of Ticlopidine therapy and how to mitigate them. An adequate discussion would include not only information about the frequency and potential severity of adverse events, but also

information about the role that clinical observation and blood monitoring can play in preventing/minimizing their clinical severity. The discussion should include information about the following known adverse events:

(i) Neutropenia/agranulocytosis;

(ii) Thrombotic thrombocytopenic purpura (TTP); and

(iii) Aplastic anemia.

c. Information delineating the schedule for blood and clinical monitoring during the first three months of treatment, and describing the steps to be taken should the results of such monitoring be abnormal.

d. A statement reinforcing the need for all health-care professionals to report observed serious and fatal adverse events with Ticlopidine administration to MedWatch.

Teva plans to implement this program by the following means:

1. Direct mailing to key physicians, pharmacists, and other health-care professionals.

2. Publication of educational information in selected, well recognized medical journals targeting health-care professionals who are in a position, in a given health-care system to educate patient and/or monitor compliance.

3. A web site providing on-line, continuing educational information. The web site address will be referenced in the direct mailing and publications.

Teva also commits to provide, at the time of product marketing, details of the educational program plan. This report will cover the range of activities that constitute the program and will include items such as timelines, target audiences and the modes of dissemination of the educational materials, web site identification, and copies of extant educational materials. In addition, Teva commits to provide a brief summary of the implementation efforts, as well as any other relevant data, associated with the educational program in each annual report.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental

application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research