ANDA 75-665 July 31, 2000

TEVA Pharmaceuticals USA
Attention: Deborah A. Jaskot
1510 Delp Drive
PO Box 247
Kulpsville, PA 19443

Dear Madam:

This is in reference to your abbreviated new drug application dated July 7, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Extended-Release Tablets, 400 mg, 500 mg, and 600 mg.

Reference is also made to your amendments dated August 17, September 24, October 4, October 29, December 2, December 9, and December 13, 1999; and January 24, March 30, April 14, May 22, June 20, July 20, and July 24, 2000.

The listed drug product (RLD), Lodine XL Extended-release Tablets of Wyeth Ayerst Laboratories, Inc. is subject to a period of patent protection which expires on April 30, 2008. Your application contains a patent certification to U.S. patent 4,966,768 under Section 505(j)(2)(A)(vii)(IV) of the Act. 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 505 (j)(2)(B)(i) is received. You have notified FDA that TEVA Pharmaceuticals USA 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 Pharmaceuticals USA within the statutory forty-five day period.

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. Please note that because of the unique (split) exclusivity issues associated with this drug product, the Agency is unable to approve all three strengths at this time. **Accordingly, the application is approved ONLY with respect to the 500 mg and 600 mg strengths**. The Division of Bioequivalence has determined your Etodolac Extended-Release Tablets, 500 mg and 600 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lodine® XL Extended-release Tablets, 500 mg and 600 mg, respectively, of Wyeth Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> Dissolution testing should be conducted in 1000 mL of phosphate buffer, pH 7.4 at 37 degrees C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following "interim" dissolution specifications:
>
> Between [ ] hours;
> between [ ] hours;
> between [ ]hours; and
> not less than [ ] hours.
>
> The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted to the annual report when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Special Supplement – Changes Being Effected.

However, due to the regulatory issues associated with the 180-day generic drug exclusivity which are discussed at the conclusion of this letter, **the 400 mg strength shall be deemed to be tentatively approved** and will not receive final approval until all exclusivity issues are satisfactorily resolved.

Under section 505(A) of the Act, certain changes in the conditions described in this abbreviated application for the 500 mg and 600 mg strengths require an approved supplemental application before the change may be made.

We note that with respect to the 500 mg and 600 mg strengths of this drug product, TEVA Pharmaceuticals USA (TEVA) was the first applicant to submit a substantially complete ANDA with a Paragraph IV certification. Therefore, TEVA is eligible for 180-days of marketing exclusivity for both the 500 mg and 600 mg strengths. Such exclusivity will begin to run either from the date TEVA begins commercial marketing of the 500 mg and 600 mg strengths, or from the date of a decision of a court finding the patent invalid or not infringed, whichever event occurs earlier [Section 505(j)(5)(B)(iv)]. A court decision that can trigger the beginning of exclusivity is a decision of a court from which no appeal may be taken (which might not be the one from the district court). With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of the 500 mg and 600 mg strengths of this drug product in a prompt manner.

If you have questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Post-marketing reporting requirements for this abbreviated application for the 500 mg and 600 mg strengths 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 the 500 mg and 600 mg strengths of the Etodolac Extended-Release Tablets.

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 for the 500 mg and 600 mg strengths. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or 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.

With respect to the tentative approval of the 400 mg strength of this drug product, our decision is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

We are unable to grant final approval to the 400 mg strength at this time because an abbreviated application for Etodolac Extended-Release Tablets, 400 mg, containing a Paragraph IV Certification was accepted for filing by OGD prior to the filing of your application. Accordingly, your application for the 400 mg strength will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the Agency receives notice of the first commercial marketing of the 400 mg strength under the previous application, or the date of a court decision described under Section 505(j)(5)(iv), whichever event occurs earlier (Section 505(j)(5)(B)(iv)). We refer you to the Agency's recently issued guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Because the Agency is granting tentative approval status under this application to the 400 mg strength, you must submit a supplemental application to provide for its full approval. The Agency will provide written notice of the information needed to determine the earliest possible final approval date of your supplemental application for the 400 mg strength under section 505(j)(5)(B)(iv) as soon as such information becomes available. The supplemental application, which must be submitted for prior approval at least 60, but not more than 90 days prior to the date you believe the 400 mg strength will be eligible for final

approval, should include updated information such as final-printed labeling, and chemistry, manufacturing and controls data as appropriate. Alternatively, a prior approval supplement should be submitted to request final approval of the 400 mg strength and stating that no changes have been made to the application since the date of this letter.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the supplemental application will be made.

In addition to, or instead of the supplemental application referred to above, the Agency may at any time prior to final approval, request that you submit an informational document containing the information stated above.

Failure to submit the supplemental application or informational document may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter for the 400 mg strength.

The 400 mg strength of Etodolac Extended-Release Tablets may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of the 400 mg strength before the final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, the 400 mg strength of the drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book").

The supplemental application should be clearly designated as a prior approval supplement in your cover letter. Because of the unique circumstances associated with the exclusivity for this drug product, you may request that the supplemental application be granted "expedited review" status. Before you submit the supplement, please contact Ms. Elaine Hu, Project Manager, at (301) 827-5754, for further instructions.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve and deficiencies associated with the validation process that may be identified.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research