ANDA 75-189 May 26, 2000

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 August 18, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Nabumetone Tablets, 500 mg and 750 mg.

Reference is also made to the Tentative Approval letter issued on December 24, 1998, and to your amendments dated December 17, 1997; February 9, 1999; and January 11, February 22, and May 1, 2000.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Please note that because of the unique exclusivity issues associated with this drug product, the agency is unable to approve both strengths at this time. **Accordingly, with respect to the 500 mg strength only, the application is approved.** The Division of Bioequivalence has determined that your Nabumetone Tablets, 500 mg, to be bioequivalent and therefore therapeutically equivalent to the listed drug (Relafen Tablets, 500 mg, of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

However, due to regulatory issues associated with 180-day generic drug exclusivity which are discussed at the conclusion of this letter, **the 750 mg strength shall remain tentatively approved** and will not receive final approval until all exclusivity issues are satisfactorily resolved.

The listed drug product (RLD) noted above and referenced in your application is subject to a period of patent protection which expires on December 13, 2002, (U.S. Patent No. 4,420,639 [the '639 patent]). Your application contains a patent certification 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 '639 patent or that the patent is otherwise invalid. You further informed the agency that litigation is currently underway in the United States District Court for the District of Massachusetts involving a challenge to the '639 patent (SmithKline Beecham Corporation, and Beecham Group, p.l.c. v. Teva Pharmaceuticals USA, Civil Action No. 97 CV12541 RCL). Today's approval is based upon the Agency's recognition that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application for the 500 mg strength require an approved supplemental application before the change may be made.

We note that with respect to the 500 mg strength only 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 market exclusivity for this strength. Such exclusivity will begin to run either from the date Teva begins commercial marketing of the 500 mg strength, 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 C.F.R. 314.107(c)(4). The Agency expects that you will begin commercial marketing of the 500 mg strength 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 strength are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the 500 mg strength of Nabumetone 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. 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

With respect to the tentative approval of the 750 mg strength of this drug product, our decision to continue the tentative approval status 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 750 mg strength at this time because an abbreviated application for Nabumetone Tablets, 750 mg, containing a Paragraph IV Certification was accepted for filing by OGD prior to the filing of your application. Accordingly, your application for the 750 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 750 mg strength under the previous application, or the date of a court decision described under section 505(j)(5)(B)(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 continuing the tentative approval status under this application for the 750 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 750 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 750 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 750 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 750 mg strength.

The 750 mg strength of Nabumetone 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 750 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 750 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 exclusivity for this drug product, you may request that the supplemental application be granted “expedited review” status. Before you submit the supplement, please contact Ruby Yu, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

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