CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125294Orig1s000

Trade Name:

Generic Name: Tbo-filgrastim

Sponsor: Sicor Biotech, UAB

Approval Date: August 29, 2012

Indications: For the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

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APPLICATION NUMBER:

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125294/0 **BLA APPROVAL**

Sicor Biotech, UAB
Attention: Diana Landa, M.S. – Authorized U.S. Representative
Director, Regulatory Affairs
Teva Pharmaceuticals, U.S.A.
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Landa:

Please refer to your Biologics License Application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351(a) of the Public Health Service Act for tbo-filgrastim.

We acknowledge receipt of your amendments dated through August 29, 2012.

The February 29, 2012, submission constituted a complete response to our September 29, 2010, letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1803 to Sicor Biotech UAB, Vilnius Lithuania, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product tbo-filgrastim. Tbo-filgrastim is indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tbo-filgrastim drug substance at Sicor Biotech UAB in Vilnius, Lithuania. The final formulated product will be manufactured, filled, labeled, and packaged at Teva Pharmaceutical Industries, Ltd, Kfar Saba, Israel. You may label your product with the proper name, tbo-filgrastim. You will market it in 300 mcg/0.5 mL and 480 mcg/0.8 mL pre-filled syringes.

DATING PERIOD

The dating period for tbo-filgrastim shall be 36 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of tbo-filgrastim to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of tbo-filgrastim, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on August 27, 2012 with the minor editorial revision to include the U.S. License No 1803 where applicable on all carton and container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed**

Carton and Container Labels for approved BLA 125294/0." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for tbo-filgrastim was not referred to an FDA advisory committee because this biologic is not the first in its class.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages less than 1 month because necessary studies are impossible or highly impracticable. This is because there are too few pediatric patients with this indication to be included in such a study.

We are deferring submission of your pediatric studies for ages 1 month to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study, required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act, is a required postmarketing trial. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required study is listed below.

PMR-1**:** Phase 2 trial in 50 pediatric patients 1month to 16 years of age to evaluate pharmacokinetics, pharmacodynamics, and safety data in patients with solid tumors without bone marrow involvement. Submit the protocol for Agency review and

concurrence prior to beginning the trial and in advance of the "final protocol submission" date so that agreement on the essential trial elements can be reached.

Draft Protocol Submission: 02/2013
Final Protocol Submission: 06/2013
Trial Completion: 06/2016
Final Report Submission: 12/2016

Submit the protocol to your IND 103188, with a cross-reference letter to this BLA.

Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of immunogenicity which could lead to impaired host immunity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR-2 To develop validated screening and confirmatory assays to assess for the presence of anti-tbo-filgrastim antibodies. The validation of the assay should include the sensitivity and specificity for detection of anti-tbo-filgrastim antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF).

The timetable you submitted on August 29, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2012
Study Completion: 02/2013
Final Report Submission: 04/2013

PMR-3 To develop a validated assay for identification of anti-product antibodies that neutralize the bioactivity of tbo-filgrastim. The validation of the assay should include the sensitivity and specificity for detection of anti- tbo-filgrastim antibodies that are also cross-reactive with and neutralize the bioactivity of native human granulocyte colony stimulating factor (G-CSF).

The timetable you submitted on August 29, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2012
Study Completion: 03/2013
Final Report Submission: 05/2013

PMR-4 To conduct an assessment for the presence of anti- tbo-filgrastim and anti-native human G-CSF binding antibodies using the validated assays developed under PMR 2 in at least 426 patients enrolled/to be enrolled in one or more clinical trials, as a substudy.

The timetable you submitted on August 29, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2013
Study Completion: 08/2014
Final Report Submission: 10/2014

PMR-5 To conduct an assessment for neutralizing antibodies using the validated assay developed under PMR 3 in all patients with binding antibodies to tbo-filgrastim or native G-CSF and in all patients with evidence of unexplained, persistent neutropenia. Sicor should provide a listing of the clinical trials in which this assessment will be conducted.

The timetable you submitted on August 29, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2013
Study Completion: 08/2014
Final Report Submission: 10/2014

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of QT prolongation which could lead to serious heart rhythm changes.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR-6 Conduct a clinical trial per ICH E14 to assess the potential for tbo-filgrastim to prolong the QT interval. Submit the protocol for review before starting the trial.

The timetable you submitted on August 29, 2012 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2012
Trial Completion:	11/2013
Final Report Submission:	06/2014

Submit the protocols to your IND 103188, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

In addition, we acknowledge your written commitments as described in your letter of August 29, 2012, as outlined below:

PMC-7 To submit data on [redacted] (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed [redacted] (b) (4) action limits of [redacted] (b) (4) prior to [redacted] (b) (4) in a CBE-30 supplement

Study Completion:	12/2016
Final Report Submission:	03/2017

PMC-8 To submit winter shipment data from the shipping qualification study in a CBE-0 supplement

Study Completion: 01/2013
Final Report Submission: 05/2013

PMC-9 To submit the following data obtained after implementation of changes made to improve microbial control in the drug substance manufacturing process:

a. In-process and final tbo-filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
b. Microbial control data for storage (b) (4)
c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

The information should be submitted as a CBE-30 supplement.

Final Report Submission: 09/2012

PMC-10 To verify that the SE-HPLC method can accurately detect aggregates by using an orthogonal method conducted with stressed drug substance and drug product samples

Final Report Submission: 03/2013

PMC-11 To characterize, using orthogonal methods, and monitor, throughout the dating period, sub-visible particulates (SVPs) in the range between (b) (4) and to propose an appropriate control strategy based on the risk to product quality, safety, and efficacy

Final Report Submission: 03/2013

PMC-12 To conduct a validation study for a quantitative peptide map method for release and stability testing and set appropriate release and stability specifications for the quantitative peptide map based on the analytical capabilities, clinical trial experience, and manufacturing history.

Final Report Submission: 03/2013

PMC-13 To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product and/or (b) (4) in the final container closure system using methods that are suitably validated for its intended purpose.

Final Protocol Submission: 10/2012
Study Completion: 02/2013
Final Report Submission: 06/2013

PMC-14 To formulate drug product, at laboratory scale, using polysorbate 80 (b) (4) and evaluate the effects of the polysorbate 80 on product quality over time.

Study Completion: 03/2016
Final Report Submission: 05/2016

Submit clinical protocols to your IND 103188 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301)-796-9634.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
08/29/2012