

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125164

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: **BL 125164/0**

NOV 14 2007

Hoffman La-Roche
Attention: Krishnan Viswanadhan, Pharm.D.
Associate Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Dr. Viswanadhan:

We have approved your biologics license application (BLA) for methoxy polyethylene glycol-epoetin beta effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, methoxy polyethylene glycol-epoetin beta under your existing Department of Health and Human Services U.S. License No. 0136. Methoxy polyethylene glycol-epoetin beta is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

Under this license, you are approved to manufacture methoxy polyethylene glycol-epoetin beta drug substance at Roche Diagnostics GmbH in Penzberg, Germany. The final formulated product in vials will be manufactured and filled at Hoffman-La Roche, Ltd., Basel, Switzerland. Labeling and packaging will be performed at Hoffman-La Roche, Ltd., Kaiseraugst, Switzerland. The final formulated product in pre-filled syringes will be manufactured and filled at Roche Diagnostics GmbH, Mannheim, Germany. Labeling and packaging will be performed at _____

You may label your product with the proprietary name Mircera[®] and may market it in single-use vials containing 50, 100, 200, 300, 400, 600 or 1000 mcg/mL, and prefilled syringes containing 50, 75, 100, 150, 200 or 250 mcg/0.3 mL, and 400, 600 or 800 mcg/0.6 mL methoxy polyethylene glycol-epoetin beta.

The dating period for methoxy polyethylene glycol-epoetin beta shall be 24 months from the date of manufacture when stored at 2^o to 8^oC. The data of manufacture shall be defined as the date of final _____ of the formulated drug product. The dating period of your drug substance shall be _____ when stored at _____. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of methoxypolyethylene glycol-epoetin beta 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of methoxy polyethylene glycol-epoetin beta, or in the manufacturing facilities.

Your application was not referred to an FDA advisory committee for review for the following reasons: The safety considerations for approved Erythropoiesis-Stimulating Agents (ESAs) were discussed at a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 11, 2007. The committees provided recommendations regarding the labeling for all ESA products and these recommendations were incorporated into the previously approved ESA labels, as well as the label for your product. Furthermore, clinical studies of your product were similar in design to previously approved products in the ESA class and your product's efficacy did not pose unique concerns in the indicated patient population, beyond the issues generally applicable to ESAs. In addition, evaluation of your product's safety when used in the treatment of the anemia due to chronic renal failure did not reveal particular safety issues that were unexpected for a member of the ESA class, when used for this specific indication.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for neonates through 4 years and deferring submission of your pediatric studies for ages 5 to 17 years until December 2012.

We acknowledge your written commitments as described in your letters of August 13, 2007, October 16, 2007, and November 8, 2007 as outlined below:

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

Your deferred pediatric studies required under the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 601.70. These commitments are listed below.

1. To conduct a multi-center, dose-finding study to determine the optimum starting dose of intravenously administered methoxy polyethylene glycol-epoetin beta when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have chronic kidney disease and are undergoing dialysis.
The protocol for this study has been submitted.
Patient enrollment will begin by July 31, 2008.
The final study report will be submitted by October 30, 2009.

2. To conduct a multi-center, randomized, controlled, parallel-group study to confirm the optimal methoxy polyethylene glycol-epoetin beta dosage when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have chronic kidney disease, inclusive of patients undergoing dialysis as well as patients who are not undergoing dialysis.
The protocol for this study has been submitted.
Patient enrollment will begin by May 31, 2010.
The final study report will be submitted by April 30, 2012.

Submit final study reports to this BLA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated “**Required Pediatric Study Commitments**”.

3. To conduct a phase 4, randomized, controlled, open label, multicenter parallel group study to assess the all cause mortality and cardiovascular morbidity in anemic patients with chronic kidney disease who are on dialysis and not undergoing dialysis. The study will enroll patients with a broad range of C-reactive protein blood concentrations and will randomize patients to treatment with either methoxy polyethylene glycol-epoetin beta or another erythropoiesis-stimulating agent.
The final study protocol will be submitted by February 29, 2008.
Patient enrollment will begin by July 31, 2008.
The final study report will be submitted by September 29, 2012.

Postmarketing Study Commitments not subject to reporting requirements of 21 CFR 601.70.

4. To provide comprehensive assay validation package for the neutralizing antibody assays. In addition to standard validation parameters the validation submission will include:
 - a. The rationale and supporting data for the following:
 - proposed criteria that designate samples as positive or negative in the neutralizing assay.
 - the system suitability criteria.
 - b. A description of the negative control that will be used in routine running of the assay as well as supporting qualification data.
 - c. The assay standard operating procedure (SOP) document.

The assay validation package will be submitted as a supplement to this BLA, by June 30, 2008.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL 125164. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125164. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments.

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cder/guidance/5569fnl.htm>) for further information.

Under 21 CFR Part 208, we have determined that this product poses a serious and significant public health concern requiring the distribution of a Medication Guide. Methoxy polyethylene glycol-epoetin beta is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product and FDA hereby approves the draft Medication Guide you submitted on November 9, 2007. Please note that:

- this Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18) or 21 CFR 201.80(f)(2)];
- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];
- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)].

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 the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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 www.fda.gov/medwatch/report/mmp.htm.

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 the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission “Product Correspondence – Final SPL for approved STN BL 125164/0.”

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

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

Sincerely,

A handwritten signature in black ink that reads "Richard Pazdur, MD". The signature is written in a cursive style with a large, prominent "R" at the beginning.

Richard Pazdur, M.D.

Director

Office of Oncology Drug Product

Center for Drug Evaluation and Research

Attachment: Physician Label
Medication Guide
Patient Instructions for Use for Vials
Patient Instructions for Use for Pre-filled Syringes