

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125164

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: November 8, 2007

From: Susan Kirshner *Susan Kirshner 11/8/07*

Through: Amy Rosenberg, Director, DTP *Amy Rosenberg 11-8-07*

Subject: Immunogenicity review for BLA 125164

Product: PEG-EPO

Sponsor: Hoffmann – La Roche

Indication: Anemia associated with chronic kidney disease

Deadlines: Mid cycle meeting – October 16, 2006

First action – May 17, 2007

Recommendations:

1. I recommend that the assays to detect binding antibodies be approved. The assay to detect binding antibodies has adequate sensitivity and specificity. Although at early post-dose time points it is likely that serum concentrations of drug are high enough to interfere with the anti-RO0503821 (PEG-EPO, Mircera) antibody assay, they are unlikely to be high enough to interfere with the anti-EPO (unmodified Epo) antibody assay, which is a more sensitive assay and is less affected by drug interference.
2. No patients taking study drug developed anti-RO0503821 or anti-EPO antibodies while participating in the study. One patient had low level (~6 ng/ml) of anti-EPO antibodies on day 0. This patient tested sero-positive on days 90 and 365 but not on days 197 and 281. On-board drug is unlikely to have resulted in patients consistently testing negative for binding antibodies for reasons elaborated in the review below. Therefore I recommend approval of the following labeling language:

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving other ESAs during post-marketing experience [see Warnings and Precautions (5.5)]. Compared to SC administration, the IV route of administration may lessen the risk for development of antibodies to Mircera.

In 1789 patients treated with Mircera in clinical studies, antibody testing using an enzyme-linked immunosorbent assay (ELISA) was conducted at baseline and during treatment. Antibody development was not detected in any of the patients.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Mircera with the incidence of antibodies to other ESAs may be misleading.

3. **At early post-dose time points, on-board drug levels can be high enough to interfere with the detection of binding antibodies. Therefore, in suspected PRCA cases, serum samples should be obtained after at least 5 half lives (~672 h or 1 month). I recommend that the underlined language below be inserted into the PRCA section of the label:**

“5.5 ... Any patient who develops a sudden loss of response to Mircera, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of the altered hemoglobin response, including evaluation for the development of neutralizing antibodies to erythropoietin [see Warnings and Precautions (5.6)]. Serum samples should be obtained at least a month after the last Mircera administration to prevent interference of Mircera with the assay...”

- 4.



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Background

Description of RO0503821

This BLA is for approval of RO0503821 (methoxy polyethylene glycol-epoietin beta) for the treatment of anemia associated with chronic renal disease both for patients on dialysis and patients not on dialysis. In this review I evaluate the assays used to test for binding and neutralizing Abs to erythropoietin (EPO) in patient sera. I will also evaluate the immunogenicity data from the pivotal trials and throughout development.

In humans, EPO is primarily produced by the kidney. EPO has a non-redundant role in erythropoiesis by stimulating bone marrow progenitor cells. In patients, neutralizing antibodies to erythropoietin have caused pure red cell aplasia (PRCA), a life threatening anemia. It is rare for EPO treated patients to develop neutralizing antibodies. Nevertheless, because the outcome of such antibodies is so serious, it is crucial to have good assays to measure binding and neutralizing activity in patient sera.

RO0503821 is synthesized by chemically conjugating one PEG molecule with an average molecular weight of ~30kDa to EPO beta via an amide bond. The recombinant human EPO portion of the molecule is the active substance of Recorman/Neorecorman, which is approved in a number of EU countries and Canada, but not in the US.

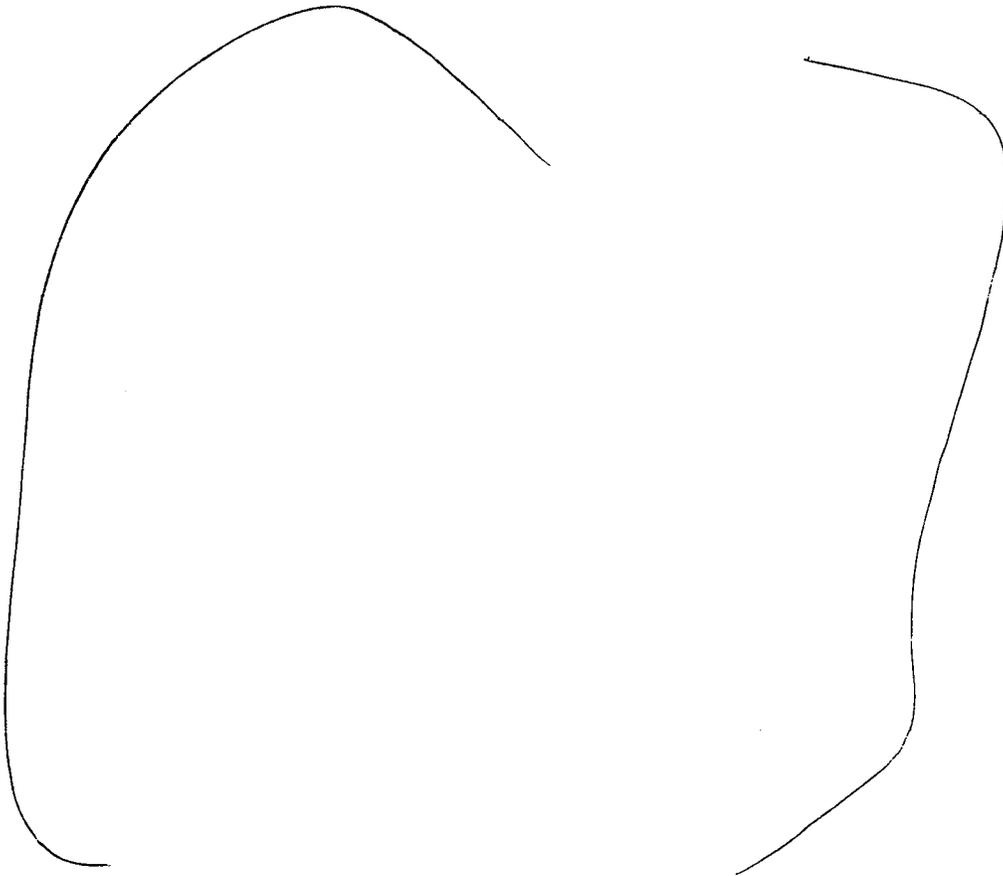
EPO is a 165 amino acid glycoprotein, with a molecular weight ranging from _____
_____ to 30,000 Da (fully glycosylated).



Results of Immunogenicity Studies

According to the Sponsor, 1789 chronic kidney disease patients treated with RO0503821 were tested for the presence of antibodies. The Sponsor validated two assays: one to detect anti-EPO antibodies and one to detect anti-RO0503821 antibodies. Anti-RO0503821 antibody tests were performed during phase 2 trials at baseline, during treatment and at follow-up. In phase 3 studies anti-RO0503821 and anti-EPO antibodies assessments were performed every three months. It should be noted that all patients were tested at each immunogenicity time point using both the anti-EPO and anti-RO0503821 antibody assays.

According to the Sponsor, no RO0503821 treated patients developed new antibodies during the course of the trials. One patient who received RO0503821 had detectable levels of antibodies to erythropoietin (the limit of quantification of the method to detect anti-EPO antibodies is 5 ng/ml) at baseline, day 90 and day 365 (range 6.09 to 6.99 ng/ml; treatment period was 52 weeks). This patient did not show lack of treatment effect.



The anti-EPO assay validation studies (reviewed in detail below) showed that:

- _____

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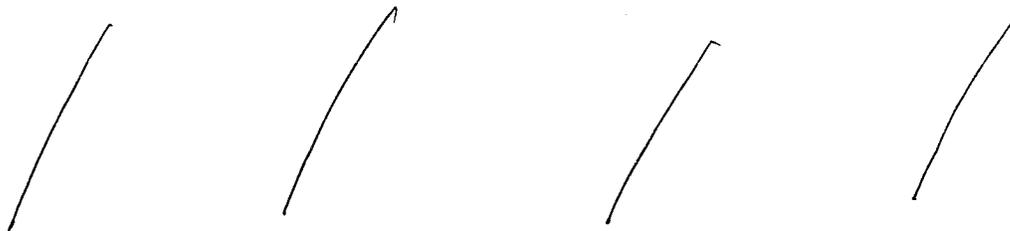


MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Ingrid Markovic, Ph.D., Quality Reviewer, DTP/OBP/OPS/CDER *Ingrid*
TO: BLA STN # 125164 file *11/6/07*
THROUGH: Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER *Barry*
Dov Pluznik, Ph.D., CMC Chair, DTP/OBP/OPS/CDER *11-6-07*
SPONSOR: Hoffmann-La Roche Inc.
PRODUCT: Mircera® (pegserepoetin alfa, RO0503821)
SUBJECT: Review of sections of BLA STN # 125141 pertaining to Extractable and leachable studies performed on the final container closure system.

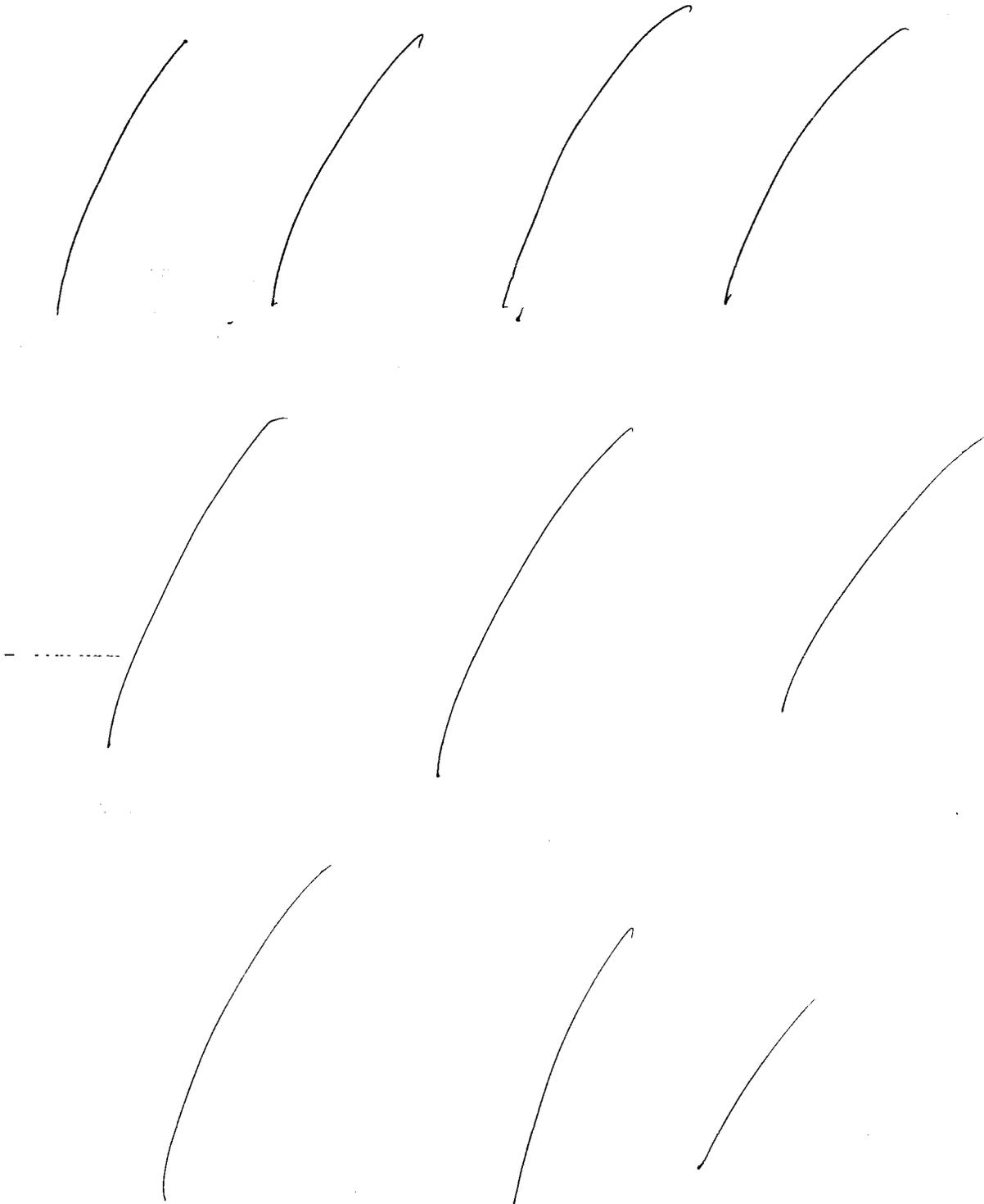
I. GENERAL OVERVIEW

The Sponsor performed a very limited analysis of extractable and leachable compounds released from the final container closure system (i.e., vials and prefilled syringes, PFS).



The Sponsor used _____ analysis for the assessment of leachables. These are reproducible methods capable of detecting, quantifying and identifying a wide range of volatile, semi-volatile and non-volatile compounds. Still, it is recommended that a clarification be sought from the Sponsor regarding rationale for their extraction strategy. Leachable testing was performed in vials placed on stability at 5°C and 25°C after 6 months of storage and at 5°C after 24 months of storage. Based on these studies, leachables detected in vials seem to be at levels below the concentration thresholds for organic solvents that would pose safety risks according to the ICH Q3C recommendation. For the class of compounds classified as low MW organic compounds, where there are no ICH recommendations (except for the analogue of N,N, Dibutyl formamide, limit 880 ppm), the Sponsor indicated that the total amount of the organic compounds does not exceed the _____ level (i.e., corresponds to _____ day limit for genotoxic impurities) under all storage temperatures and times. The risks therefore appear reasonably low for leachable substances eluting from vial components. Volatile leachables eluting from PFS components were studied under real-time (5°C after 6, 12, 18 and 24 months) and accelerated conditions (25°C/60%RH and 30°C/65%RH) and were at the limit of assay detection. It is of note that syringes present a greater safety risk for leachable substances compared to vials due to

release of _____ in the final product. A number of limitations were noted in the study that are listed below as follows:



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MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Ingrid Markovic, Ph.D., Quality Reviewer, DTP/OBP/OPS/CDER *Ingrid*
TO: BLA STN # 125164 file *11/6/07*
THROUGH: Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER *BC*
Dov Pluznik, Ph.D., CMC Chair, DTP/OBP/OPS/CDER *11-8-07*
SPONSOR: Hoffmann-La Roche Inc.
PRODUCT: Mircera® (pegserepoetin alfa, RO0503821)
SUBJECT: Review of Sponsor's responses to Agency's inquiry regarding
Extractables and leachables studies submitted on August 17, 2007.

Recommendation: The Sponsor's responses and their analysis of extractable and leachable substances in the final container closure systems (i.e., vials and prefilled syringes) seem acceptable with no unnecessary risks incurred to patient safety and product quality. Therefore, this submission appears satisfactory from the extractables and leachables perspective.

Review of comments conveyed to the Sponsor and their responses

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DATE: May 18, 2007, Updated October 3, 2007; Final revision November 5, 2007
FROM: Dov H. Pluznik, Ph.D., CMC Reviewer, DTP/OBP/OPS/CDER
TO: BLA STN # 125164 file
THROUGH: Amy Rosenberg, MD, Director, DTP/OBP/OPS/CDER
Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER
SPONSOR: Hoffmann-La Roche Inc.
PRODUCT: Mircera® (methoxy polyethylene glycol-epoetin beta)
SUBJECT: The Chemistry Executive Summary

JP 11/7/07
OSL 11-7-07
EC 11-7-07

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125164 methoxy polyethylene glycol-epoetin beta manufactured by Hoffmann-La Roche. The data submitted in this application support the conclusion that the manufacture of methoxy polyethylene glycol-epoetin beta is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Although a number of deficiencies in the original application were noted, during the subsequent review (of the response to our CR letter) outstanding CMC issues were resolved.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- General:** methoxy polyethylene glycol-epoetin beta is comprised of erythropoietin beta with an amide bond between either the N-terminal amino groups or the ϵ -amino group of lysine, predominately Lys₅₂ and Lys₄₅ and methoxy polyethylene glycol butanoic acid. This results in a molecular weight of approximately 60,000 daltons for methoxy polyethylene glycol-epoetin beta, and the PEG moiety having an approximate molecular weight of — daltons.

The Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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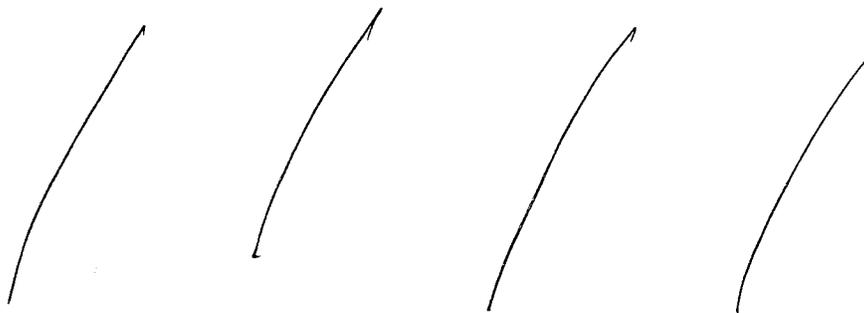
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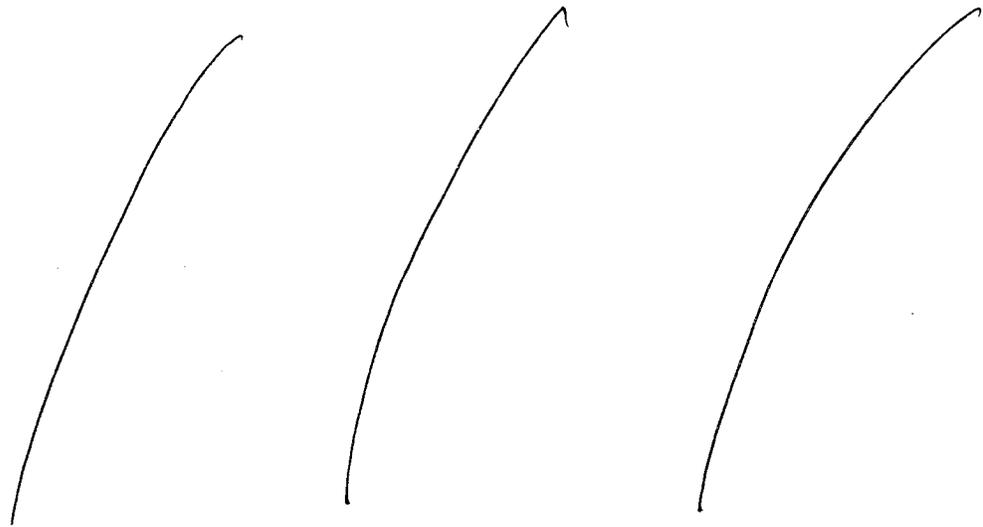
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- **Biological activity:** The biological activity of methoxy polyethylene glycol-epoetin beta resides in the EPO moiety of the product. EPO is a recombinant form of erythropoietin, the hormone responsible for the maintenance of erythropoiesis. The molecule binds to and activates EPO receptors on erythroid progenitor cells that develop into mature erythrocytes. EPO increases reticulocyte counts, hemoglobin levels and hematocrit in a dose proportional manner. Although a critical role of EPO is the regulation of red blood cell production, EPO and its receptors have been localized to many non-hematopoietic tissues and cells, including the central nervous system, endothelial cells, solid tumors, the liver and uterus. In particular, expression of EPO receptors in cancer cells has generated much concern that administration of EPO to patients with breast, head and neck and other cancer cells may promote tumor growth via activation of the EPOR and induction of cell proliferation and/or angiogenesis. Indeed, several clinical trials using unapproved dosing regimens reported increased disease progression and decreased survival associated with the administration of ESAs in patients with cancer of the breast, non small cell lung carcinoma and squamous cell carcinoma of the head and neck. Several studies have also indicated EPO may interact with unique receptors expressed in neural tissue. EPO is believed to be a pleotropic cytokine that is part of the biological response to hypoxia and has important biological effects outside of hematopoiesis. These other biological activities must be considered when evaluating critical product attributes and their relationship to safety and efficacy.
- **Potency Assays to Measure Activity.** The product is designed to stimulate erythropoiesis in patients with anemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis. The determination of the EPO bioactivity is based on measurement ←



- **Drug Product Presentation:** Mircera™ is supplied as a clear aqueous sterile liquid for IV and SC administration. It is supplied in glass vials with a closure of a rubber stopper and an aluminium cap (fitted with a plastic flip-off disc). It is also supplied in pre-filled 1 mL glass syringes (PFS). The closure of the syringe consists of a plunger stopper made from rubber and a rubber tip-cap. Vials are for single use IV and SC administration while the PFS are only for SC administration.

- a. Single-dose **vials** are available containing 50, 100, 200, 300, 400, 600 or 1000 µg/mL of methoxy polyethylene glycol-epoetin beta per mL/vial. Injectable solutions of methoxy polyethylene glycol-epoetin beta are formulated in an aqueous solution containing sodium phosphate, sodium sulphate, mannitol, methionine and poloxamer 188.

The solution is clear, colorless to slightly yellowish and the pH is 6.2 ± 0.2 . The drug product solutions of the seven dosage strengths are identical in their qualitative composition. Quantitatively, they differ in their content of DS according to the dosage strengths. The composition of these drug products is the same as employed in pivotal clinical studies up to date.

- b. Single-dose **pre-filled syringes** (PFS) are available containing 50, 75, 100, 150, 200, 250 µg/0.3 mL and 400, 600 or 800 µg/ 0.6 mL per PFS of methoxy polyethylene glycol-epoetin beta. Injectable solutions of methoxy polyethylene glycol-epoetin beta are formulated in an aqueous solution identical to the vial formulation. To reduce the risk of accidental needle sticks to users, each pre-filled syringe is equipped with a needle guard that covers the needle during disposal. The drug product solutions of the nine dosage strengths are identical in their nominal qualitative composition. Quantitatively, they differ in their content of DS according to the different dosage strengths. The composition of these drug products is the same as employed in pivotal clinical studies up to date.

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F. Basis for Approvability Recommendation

Mircera™ is manufactured by a — process with precautions for contamination by cell substrate or adventitious agents. Mircera™ is manufactured consistently, resulting in a safe and potent product, and should be approved for the proposed indication.

May 18, 2007; Updated: October 3, 2007; Revised November 5, 2007



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MAY 16 2007

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: May 14, 2007
To: Administrative File, STN125164/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ TFRB, HFD-328
Through: Michelle Clark-Stuart, M.S., CDER/OC/DMPQ/TRFB, HFD-328
Subject: New BLA for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis
US License # 0136
Applicant: F. Hoffman La Roche, LTD
Facilities: Drug Substance – Pharmaceutical Biotech Production, Roche Diagnostics GmbH, D-82377, Penzberg, Germany, FEI 3002806560
Drug Product – vials – F. Hoffmann-La Roche LTD, CH-4070 Basel, Switzerland, FEI 3002807200
Drug Product – Pre-filled syringes – Roche Diagnostics GmbH, D-68305 Mannheim, Germany, FEI 3002806559
Product: MIRCERA® (pegserepoetin alfa)
Indication: Treatment of anemia of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis.
Dosage: Sterile injectable solution in single use vials and in pre-filled syringes
Due date: 19 May 2007

DFH 5/16/07
myls 5/16/07

Recommendation: The application, as amended, is recommended for approval from sterility assurance and microbiology product quality perspective.

Review Summary

F. Hoffman-La Roche submitted this BLA to license the product, MIRCERA® (pegserepoetin alfa), and the associated Drug Substance and Drug Product manufacturing processes. Drug Substance manufacturing is conducted by Roche diagnostics GmbH, Pharma Biotechnology Production & Development in Penzberg, Germany (Roche-Penzberg). Drug Product is manufactured at F. Hoffmann-La Roche LTD, Basel, Switzerland (Roche-Basel) and at Roche Diagnostics GmbH, Mannheim, Germany (Roche-Mannheim). Drug Substance and Product testing is conducted by Roche Diagnostics, in Penzberg, Germany, and in Mannheim Germany

The BLA was submitted in an electronic Common Technical Document (CTD) format. Two amendments were submitted at the request of the Therapeutics Facility Review Branch (TFRB). The following is a list of the requested amendments and their corresponding contents:

Amendment 027 22 March 2007

Amendment 030 29 March 2007

Two manufacturing facilities were inspected: Roche-Penzberg was inspected on November 6-10, 2006 and Roche-Basel was inspected on November 13-17, 2006. No Form 483 observations were presented at the conclusion of the inspection of the Roche-Penzberg site. A number of observations were issued on FDA Form 483 on November 17, 2006. Responses to the Form 483 observation were received, reviewed, and deemed adequate by the OC/DMPQ/FIT, HFD-328.

See the Conclusion section of this review for the individual inspectional items.

Review Narrative

The BLA contains two sections for drug substance, Section 3.2.S Drug substance EPO Starting Material and 3.2.S Drug Substance-RO0503821. This review does not assess the EPO or the RO0503821 manufacturing process and controls. The information provided in the BLA was reviewed as background information for the pre-license inspection of November 6 - 10, 2006 in Penzberg with Patricia F. Hughes, Ph.D. from OC/TFRB and Dov Pluznik, Ph.D. from OBP/DTP. The Roche-Penzberg site where the drug substance is manufactured was found to be acceptable from a CGMP perspective and a Form 483 was not issued.

A brief summary of the drug substance manufacturing process is provided in the following section on drug substance.

Drug Substance

General Information: Description & Characterization

RO0503821 is a _____ erythropoietic compound that is synthesized by chemically conjugating one linear methoxy-polyethylene glycol molecule (PEG) to Epoetin beta (EPO, RO2053859).

There are _____ pegylation sites in the EPO protein, which include the N-terminal amino group and the ϵ -amino groups of lysines. _____

_____ Lys 45 and Lys 52 have been determined to be the major pegylation sites. The molecular weight of the molecule is 60 kDa.

Manufactures for EPO and drug substance RO0503821

The manufacturing sites for the drug substance are as follows:

The manufacturer of PEG reagent is:



Epoetin beta and drug substance (RO0503821 purified drug substance) manufacturing and release testing site is:

Pharmaceutical Biotech Production
Roche Diagnostics GmbH
Nonnenwald 2
D-82377, Penzberg, Germany
FEI # 3002806560

This facility was the subject of a PLI on November 6-10, 2006

The unprocessed bulk testing site is:



The Roche Penzberg site was inspected on the following dates:

- April 07-14, 2005 in a Bi-annual inspection of Interferon alfa-2a
- November 8 -12, 2004 in a pre-approval inspection for Peginterferon alfa-2a
- November 6 – 10, 2006 in a pre-approval inspection for MIRCERA®

The Roche - Penzberg site has an acceptable GMP status.

Biological activity assays for batch release testing are conducted at:

Roche Diagnostic GmbH
Galénical Operations
Sandhoffer Straße 116
68298 Mannheim, Germany
FEI # 3002806559

Or at an alternative test site:



Reviewer comments: A recommendation to register the _____ was made to the firm during and after the inspection at Roche Penzberg. It was determined that this was not a requirement for foreign laboratories (communication on May 4, 2007 with John Dietrick, OC/DMPQ/FIT).

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