

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125164

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA #: 125164/0 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 4/19/06 PDUFA Goal Date: 11/14/07 (2nd Cycle)

HFD 160 Trade and generic names/dosage form: Mircera[®] (methoxy polyethylene glycol-epoetin beta)

Applicant: Hoffman La-Roche Therapeutic Class: Hematology

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next section.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of anemia associated with chronic renal failure (CRF) including patients on dialysis and not on dialysis.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into RMS-BLA Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Waived.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 4 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Partially Waived

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 5 Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): April 30, 2012.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Deferred

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

BLA 125164/0

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If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Data Submitted and Complete.

This page was completed by:

FMA 11/14/07
Florence O. Moore
Regulatory Project Manager

cc: BLA 125164/0
Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT ROSEMARY ADDY OR GRACE CARMOUZE

(revised for TBP licensing products 9-15-2006)

STN: 125164/0
Hoffman La Roche
April 18, 2006

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

ACTION PACKAGE CHECKLIST

| Application Information | | |
|--|--------------------------------|--|
| NDA # 125164 | BLA STN# 0 NDA Supplement # | If NDA, Efficacy Supplement Type |
| Proprietary Name: Mircera Established Name: methoxy polyethylene glycol-epoetin beta Dosage Form: Solution for Injection: Intravenous [IV] or Subcutaneous [SC] | | Applicant: Hoffman La-Roche |
| RPM: Florence Moore | | Division: DMIHP Phone # 301-796-1423 |
| NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) | | 505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: |
| ❖ User Fee Goal Date | | November 14, 2007 |
| ❖ Action Goal Date (if different) | | |
| ❖ Actions | | |
| • Proposed action | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR |
| • Previous actions (specify type and date for each action taken) | | <input type="checkbox"/> None CR ltr May 18, 2007 |
| ❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews) | | <input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed |

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| ❖ Application Characteristics | |
| Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments: | |
| ❖ Application Integrity Policy (AIP) | |
| <ul style="list-style-type: none"> Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action |
| ❖ Public communications (approvals only) | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Advisory |

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| ❖ Exclusivity | |
| <ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDA: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDA: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDA: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| ❖ Patent Information (NDAs and NDA supplements only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input type="checkbox"/> Verified <input checked="" type="checkbox"/> Not applicable because _____ |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire _____ |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). | <input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

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| <p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below. (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p> | |
| Summary Reviews | |
| ❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>) | Karen Weiss 5/18/07; Dwayne Rieves 5/17/07; 11/9/07 |
| ❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>) | Included 11/8/07 |
| Labeling | |
| ❖ Package Insert | |
| • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | November 13, 2007 |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | November 8, 2007 |
| • Original applicant-proposed labeling | Included |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | |
| ❖ Patient Package Insert | |
| • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) | November 8, 2007 |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | November 8, 2007 |
| • Original applicant-proposed labeling | Included |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable | |
| Medication Guide | |
| • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) | November 8, 2007 |
| • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) | November 9, 2007 |
| • Original applicant-proposed labeling | Included |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | |
| ❖ Labels (full color carton and immediate-container labels) | |
| • Most-recent division-proposed labels (only if generated after latest applicant submission) | |
| • Most recent applicant-proposed labeling | Included |
| ❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>) | <input checked="" type="checkbox"/> DMETS Mar 14, 07; Oct 5, 06 <input checked="" type="checkbox"/> DSRCs Oct 29, 07; Apr 6, 07 <input type="checkbox"/> DDMAC Jul 7, 07; Dec 12, 06 <input checked="" type="checkbox"/> SEALD Sep 28, 2007 <input checked="" type="checkbox"/> Other reviews CMC 6/28/07 <input type="checkbox"/> Memos of Mtgs |

| Administrative Documents | |
|--|--|
| Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>) | Application Designation 4/25/07 Mid cycle Mtg Memo 10/16/06 First Comm Memo 5/9/06 Filing Memo 6/1/06 Reg Briefing Summary 3/16/07 |
| ❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>) | <input type="checkbox"/> Included |
| ❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval | |
| ❖ Pediatric Page (all actions) | <input checked="" type="checkbox"/> Included |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| ❖ Postmarketing Commitment Studies | <input type="checkbox"/> None |
| <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) | Nov 2, 2007 |
| <ul style="list-style-type: none"> Incoming submission documenting commitment | Nov. 8, 2007 |
| ❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons) | Included |
| ❖ Internal memoranda, telecons, email, etc. | Included |
| ❖ Minutes of Meetings | |
| <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) | 10/12/07 |
| <ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) | <input type="checkbox"/> No mtg Clinical- Mar 6-06; CMC- Dec 21-05 |
| <ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) | <input type="checkbox"/> No mtg Oct. 31, 2003 |
| <ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) | Application Orientation Mtg May 31-06; Reg Briefng Mar 16, 07 |
| ❖ Advisory Committee Meeting | <input checked="" type="checkbox"/> No AC meeting |
| <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available | |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | |
| CMC/Product Quality Information | |
| ❖ CMC/Product review(s) (<i>indicate date for each review</i>) | Kirshner May 8-07 Pluznik May 18,07; Nov Markovic Nov 6, 07 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ BLAs: Product subject to lot release (APs only) | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <ul style="list-style-type: none"> <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>) | |

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| | <input type="checkbox"/> Not a parenteral product |
| ❖ Facilities Review/Inspection | |
| ❖ NDAs: Facilities inspections (include EER printout) | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) | May 14, 2007 <input checked="" type="checkbox"/> Requested Nov 13, 07; May 17, 07 <input checked="" type="checkbox"/> Accepted Nov 14, 07 <input type="checkbox"/> Hold |
| ❖ NDAs: Methods Validation | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed |
| Nonclinical Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | May 14, 2007; Nov 5, 07 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | |
| ❖ Nonclinical inspection review Summary (DSI) | <input type="checkbox"/> None requested |
| Clinical Information | |
| ❖ Clinical review(s) (<i>indicate date for each review</i>) | Secondary Review May 14, 07, Nov 7, 07 Primary Review May, 07 Tertiary Review May, 2007, Nov 9, 07 |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review | See clinical review 1.3.4 |
| ❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>) | <input type="checkbox"/> None |
| Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>) | <input type="checkbox"/> Not needed |
| ❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>) | See clinical review section 5.3.5 |
| ❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>) | |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>) | <input type="checkbox"/> Not needed |
| ❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input type="checkbox"/> None requested |
| • Clinical Studies | Included |
| • Bioequivalence Studies | |
| • Clin Pharm Studies | |
| ❖ Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None Nov 13, 07; May 4, 07 |
| ❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None Nov 2, 07; May 3, 2007 |

Comment [11]:

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Moore, Florence O

From: Hughes, Patricia
Sent: Tuesday, November 13, 2007 7:53 AM
To: CDER-TB-EER
Cc: Moore, Florence O; Randazzo, Giuseppe; Hoyt, Colleen; Hughes, Patricia
Subject: Compliance check for Hoffmann-La Roche BLA 125164/0 Mircera

Please conduct the following compliance checks in support of the BLA for Mircera from Hoffmann La Roche. The PDUFA date is November 14, 2007.

Facilities:

Drug substance manufacturing and testing: Roche Diagnostics GmbH, D-82377, Penzberg, Germany, FEI 3002806560 (PAI on November 6-10, 2006)

Drug Product vials manufacturing and testing: F. Hoffmann-La Roche LTD, CH-4070 Basel, Switzerland, FEI 3002807200 (PAI on November 13-17, 2006)

Drug Product pre-filled syringes manufacturing and test lab: Roche Diagnostics GmbH, D-68305 Mannheim, Germany, FEI 3002806559

thank you.

Patricia

Moore, Florence O

From: Hoyt, Colleen
Sent: Wednesday, November 14, 2007 5:04 PM
To: Moore, Florence O; Hughes, Patricia; CDER-TB-EER
Cc: Randazzo, Giuseppe
Subject: RE: Compliance check for Hoffmann-La Roche BLA 125164/0 Mircera

There are no pending or ongoing compliance actions or investigations to prevent approval of STN 125164/0 at this time. The firm's associated with the manufacture of Mircera have been inspected and are currently in compliance with cGMPs. I will note that the establishment inspection report from the November 13-17, 2006 inspection of F. Hoffman LaRoche, Basel, SZ, has not been received at this time.

Colleen F. Hoyt
Compliance Officer
Investigations and Preapproval Compliance Branch
CDER/OC/DMPQ
(301) 827-9014
colleen.hoyt@fda.hhs.gov

From: Moore, Florence O
Sent: Wednesday, November 14, 2007 4:44 PM
To: Hughes, Patricia; CDER-TB-EER
Cc: Randazzo, Giuseppe; Hoyt, Colleen
Subject: RE: Compliance check for Hoffmann-La Roche BLA 125164/0 Mircera
Importance: High

Hi there,

The Mircera application is due today. Can you please send me a response for the action package today?

Thanks,
Florence

From: Hughes, Patricia
Sent: Tuesday, November 13, 2007 7:53 AM
To: CDER-TB-EER
Cc: Moore, Florence O; Randazzo, Giuseppe; Hoyt, Colleen; Hughes, Patricia
Subject: Compliance check for Hoffmann-La Roche BLA 125164/0 Mircera

Please conduct the following compliance checks in support of the BLA for Mircera from Hoffmann La Roche. The PDUFA date is November 14, 2007.

Facilities:

Drug substance manufacturing and testing: Roche Diagnostics GmbH, D-82377, Penzberg, Germany, FEI 3002806560 (PAI on November 6-10, 2006)

Drug Product vials manufacturing and testing: F. Hoffmann-La Roche LTD, CH-4070 Basel, Switzerland, FEI 3002807200 (PAI on November 13-17, 2006)

Drug Product pre-filled syringes manufacturing and test lab: Roche Diagnostics GmbH, D-68305 Mannheim, Germany, FEI 3002806559

thank you.

Patricia

RECORD OF TELEPHONE CONVERSATION

BLA: 125164

Today's date: November 9, 2007

Speakers: Dwaine Rieves for FDA and Krishnan Viswanadhan for Roche

I called Roche to let them know that we have shared the feedback from this morning's conversation and the review team has expressed concerns. I noted that Roche should not regard this issue as settled because _____ remains a concern. I encouraged Roche to develop a proposal. I stated that this issue may or may not be a critical discussion item for next week.

**Appears This Way
On Original**

LICENSING ACTION RECOMMENDATION

Applicant: Hoffman La- Roche STN: 125164/0

Product: Mircera (methoxy polyethylene glycol-epoetin beta)

Indication / manufacturer's change : Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis

- Approval: Summary Basis For Approval (SBA) included, Memo of SBA equivalent reviews included, Refusal to File: Memo included, Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report, Inspection of establishment, BiMo inspections completed, Review of protocols for lot no.(s), Test Results for lot no.(s), Review of Environmental Assessment, FONS I included, Categorical Exclusion, Review of labeling, Date completed, None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required, Lot no.(s) in support - not for release, Lot no.(s) for release, Director, Product Release Branch

CLEARANCE - REVIEW

Review Committee Chairperson: Date: Product Office's Responsible Division Director(s)*: Date: DMPQ Division Director*: Date:

* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

Compliance status checked: Acceptable, Hold, Cleared from Hold, Date: May 16 2007, Regulatory Project Manager (RPM) Florence Moore, Date: 10/29/07, Responsible Division Director, Date: 11-8-07

Moore, Florence O

From: Moore, Florence O
Sent: Thursday, November 08, 2007 2:58 PM
To: 'Viswanadhan, Krishnan'
Subject: PMC #4

Attachments: PMC.doc

Dear Krishnan,

Please see attached FDA proposed PMC number 4 for our discussions tomorrow 10-10:30 AM



PMC.doc (28 KB)

Regards,

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

Tel: 301-796-1423

Fax: 301-796-9849

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1

Moore, Florence O

From: Viswanadhan, Krishnan [krishnan.viswanadhan@roche.com]
Sent: Thursday, November 08, 2007 12:08 PM
To: Moore, Florence O; Rieves, Rafel
Cc: GRASS, Nutley {PDR~Nutley}; Viswanadhan, Krishnan {PDR~Nutley}
Subject: FW: T-con Request on PMCs
Importance: High

Hi Florence,

See below comments from Roche on the proposed post marketing commitments. I have highlighted in red the changes. Roche concurs with the following post marketing commitments. As discussed, We don't see a need for a teleconference, if you agree, based on these post marketing commitments. Let me know if you have any questions.

Kind Regards,
Krishnan

Krishnan Viswanadhan, Pharm.D.
Hoffmann-La Roche Pharmaceuticals
Pharma Development Regulatory
340 Kingsland Street
Nutley, NJ 07110
Telephone: (973)235-6241
Fax: (973)562-3700

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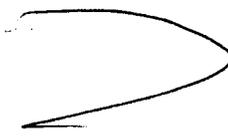
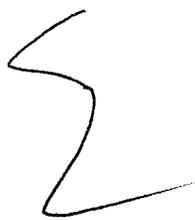
From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Thursday, November 08, 2007 9:39 AM
To: Viswanadhan, Krishnan {PDR~Nutley}
Cc: Rieves, Rafel
Subject: RE: T-con Request on PMCs

Hi Krishnan,

we need to finalize the PMC today, if your clinical reviewers are not available lets try and do this via email. We can try and schedule the t-con for Friday am if we still need it. Please try to respond to this by the end of today.

Please provide comments or your concurrence to the revised PMCs below. Also provide dates as well.

1.



2 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-2

Moore, Florence O

From: Moore, Florence O
Sent: Thursday, November 08, 2007 2:16 PM
To: 'Viswanadhan, Krishnan'
Subject: Mircera Label

Attachments: Last FDA to Roche11-8-07redline (3).doc; Last FDA to Roche11-8-07clean.doc

Dear Krishnan,

See attached FDA's final revisions to the physician label with the Med Guide (redline and clean copy) . If you concur to this please resubmit formally to the application as Roche's final PI label. As discussed earlier, I will send you the patient instructions sheets in a separate email as it is too large to send in one email.



Last FDA to Roche11-8-07redlin... Last FDA to Roche11-8-07clean...

Regards,
Florence

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

Tel: 301-796-1423
Fax: 301-796-9849

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LICENSING ACTION RECOMMENDATION

Applicant: Hoffmann-LaRoche STN: STN 125164/0

Product: Pegeserepoetin alfa

Indication / manufacturer's change:

New BLA for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis.

- Approval: Summary Basis For Approval (SBA) included, Memo of SBA equivalent reviews included, Refusal to File: Memo included, Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report, Inspection of establishment, BIMO inspections completed, Review of protocols for lot no.(s), Test Results for lot no.(s), Review of Environmental Assessment, FONSJ Included, Categorical Exclusion, Review of labeling, Date completed, None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required, Lot no.(s) in support - not for release, Lot no.(s) for release, Director, Product Release Branch

CLEARANCE - REVIEW

Review Committee Chairperson: Dov Pluznik, Ph.D. Date: 116 May 2007

Product Office's Responsible Division Director(s)*: [Signature] Date: 5/15/07

* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

- Compliance status checked: Acceptable, Hold, Cleared from Hold, Date: 16 May 2007

Regulatory Project Manager (RPM) [Signature] Date: 5/17/07

Responsible Division Director (where product is submitted, e.g., application division or DMPQ) [Signature] Date: 11-7-07

Moore, Florence O

From: Moore, Florence O
Sent: Monday, November 05, 2007 3:14 PM
To: 'Viswanadhan, Krishnan'
Subject: Mircera Label: FDA Updated Current Version

Attachments: clean11-5- 07FDA Version (5).doc

Dear Krishnan,

Please see attached the most current FDA version of the PI for your comments. Please provide your revisions/comments to the label to me no later than COB 11/7/07.



clean11-5- 07FDA
Version (5).d...

Regards,
Florence

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

*Tel: 301-796-1423
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Moore, Florence O

From: Moore, Florence O
Sent: Friday, November 02, 2007 3:14 PM
To: 'Viswanadhan, Krishnan'
Subject: RE: Immunogenicity PMC

Thanks.

From: Viswanadhan, Krishnan [mailto:krishnan.viswanadhan@roche.com]
Sent: Friday, November 02, 2007 3:00 PM
To: Moore, Florence O
Cc: GRASS, Nutley {PDR~Nutley}
Subject: RE: Immunogenicity PMC

Hi Florence,
Roche concurs. Timeline for submission of a supplement to the BLA is June 2008.

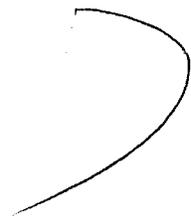
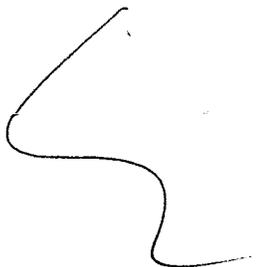
Kind Regards,
Krishnan

From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Thursday, November 01, 2007 11:48 AM
To: Viswanadhan, Krishnan {PDR~Nutley}
Subject: Immunogenicity PMC

Hi Krishnan:

FDA is proposing the immunogenicity assay below:

Proposed PMC language:



Please provide concurrence and provide the timelines (Provide dates for any protocols and final reports).

Thanks,

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

Tel: 301-796-1423

Fax: 301-796-9849

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3

RECORD OF TELEPHONE CONVERSATION

BLA: 125164/0

Product: Mircera

Sponsor: Roche

Today's date: October 29, 2007

Speakers: Cynthia Dinella and Krishnan Viswanadhan for Roche

FDA Participants: Dwaine Rieves and Florence Moore

Roche called DMIHP to give an update on the status of the Mircera patent litigation. Roche gave us their perspective on the recent development on the patent infringement case in the United States relating to Mircera. Roche indicated the patent issues with Amgen will not impact their goal of getting a FDA approval on Mircera as targeted for November 14, 2007.

Roche noted that they will be sending a letter to all investigators regarding the outcome of the patent infringement case. Roche will be requesting in the letter that all US physicians participating in clinical trials suspend enrollment of new patients. US patients that are currently enrolled will continue treatment under the provisions of the individual protocols. Enrollment will continue at all Non-US sites.

Roche indicated that they will continue to do all PMCs that have a regulatory and safety impact on the drug and would like to propose new PMCs and timelines. Roche stated that they are appealing their case in the USA courts. FDA noted that the on-going issues will not impact the FDA review and that we are on target to meet the PDUFA goal date.

Moore, Florence O

From: Moore, Florence O
Sent: Wednesday, October 24, 2007 2:01 PM
To: 'Viswanadhan, Krishnan'; Stephenson, Angela {PDR~Nutley}
Subject: Mircera PLR

Attachments: FDAWorkingDoc to Roche10-23-07 PLR.doc

Hi Krishnan,

Please note this is still a work in progress and we do not expect you to comment on this right now. Dr. Rieves is willing to talk to you about this after 3:30 today if you have any questions. If you do please provide a number where you can be reached.



FDAWorkingDoc to
Roche10-23-07...

Regards,

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

Tel: 301-796-1423

Fax: 301-796-9849

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Moore, Florence O

From: Moore, Florence O
Sent: Wednesday, October 24, 2007 7:29 AM
To: 'Viswanadhan, Krishnan'; Stephenson, Angela {PDR~Nutley}
Subject: RE: Information Request

Thanks for your quick response Krishnan.

Florence

From: Viswanadhan, Krishnan [mailto:krishnan.viswanadhan@roche.com]
Sent: Wednesday, October 24, 2007 7:22 AM
To: Moore, Florence O; Stephenson, Angela {PDR~Nutley}
Cc: Viswanadhan, Krishnan {PDR~Nutley}
Subject: RE: Information Request

Hi Florence,
Thanks for your message. See below responses to your questions:

1. FDA Question 1: What is the proper (e.g. USAN) name for this product?

As indicated in Amendment 23 of the BLA, Dated February 9, 2007, Roche is currently working with USAN Council not accepted by the USAN Council. Therefore, Roche intends to utilize the proper chemical name, methoxypolyethylene glycol epoetin beta until a final USAN name has been adopted. Hence, all labeling components (carton, container, etc.) will include the chemical name.

This approach is also consistent with the approach in Europe. Since no approved INN name is available, the chemical name is included in all labeling.

2. FDA Comment 2: Regarding the carton and vial labels DMETS finds the container and carton labels acceptable except for the 1000 mcg label. Please increase the prominence of the strength (1000 mcg) to be equally prominent as the trade name (Mircera). The white background is acceptable but the strength needs to be a bit more prominent since in the current presentation, the strength gets lost with the rest of the information on the label.

We appreciate the feedback. Roche will attempt to increase the prominence of the strength 1000 mcg based on the FDA DMETS recommendations.

3. FDA Comment 3: Per CMC comments the container and carton labels are acceptable. However, a change in the wording under the Storage section of the PI was recommended as follows: The end user may store the product at room temperature (25°C or less) for up to _____

Roche has already revised the carton/container labeling as part of Amendment 49 to note "up to" _____ Similarly, the PI submitted as part of Amendment 47 was revised to include "up to" .

Let us know if you have any questions.

Kind Regards,
Krishnan

Krishnan Viswanadhan, Pharm.D.
Hoffmann-La Roche Pharmaceuticals
Pharma Development Regulatory

10/29/2007

340 Kingsland Street
Nutley, NJ 07110
Telephone: (973)235-6241
Fax: (973)562-3700

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From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Tuesday, October 23, 2007 6:19 PM
To: Viswanadhan, Krishnan {PDR~Nutley}; Stephenson, Angela {PDR~Nutley}
Subject: Information Request
Importance: High

Hi Krishnan

What is the proper (e.g. USAN) name for this product?

Is it pegzerepoetin alfa or methoxy polyethylene glycol-epoetin beta? Also, what is on the carton/container labels? "methoxy polyethylene glycol-epoetin beta" should not be mentioned unless it is the proper name. We need to fix this on all labeling, reviews, etc.

Regarding the carton and vial labels DMETS finds the container and carton labels acceptable except for the 1000 mcg label. Please increase the prominence of the strength (1000 mcg) to be equally prominent as the trade name (Mircera). The white background is acceptable but the strength needs to be a bit more prominent since in the current presentation, the strength gets lost with the rest of the information on the label.

Per CMC comments the container and carton labels are acceptable. However, a change in the wording under the Storage section of the PI was recommended as follows: The end user may store the product at room temperature (25°C or less) for **up to** _____

Please address these two issues. We are still working on the PLR, Medguide and patient instruction sheet.

Regards,
Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903

Tel: 301-796-2050
Fax: 301-796-9849

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

OCT 22 2007

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

Dear Dr. Viswanadhan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Pegzerepoetin alfa (Mircera).

We also refer to the teleconference held on October 11, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely yours,

A handwritten signature in black ink, appearing to read "F. O. Moore".

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type C

Meeting Category: Other

Meeting Date and Time: October 11, 2007

Meeting Location: CDER WO 1419 Conf Room Bldg 22

Application Number: STN 125164/0

Product Name: Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche)

Received Briefing Package NA

Sponsor Name: Hoffman La-Roche

Meeting Requestor: Krishnan Viswanadhan, Pharm.D.

Meeting Chair: Rafel Rieves, M.D.

Meeting Recorder: Florence Moore, M.S.

Meeting Attendees:

FDA Attendees

Office of Oncology Drug Products

Division of Medical Imaging and Hematology Products

Rafel (Dwayne) Rieves, M.D., Deputy Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader

Adebayo Laniyonu, Pre-Clinical Team Leader

Yanli Ouyang, Ph.D., Pre-Clinical Reviewer

Alice Kacuba M.S.N., RAC, Regulatory Health Project Management Team Leader

Florence Moore M.S., Regulatory Health Project Manager

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader

Office of Biostatistics

Division of Biometrics V

Jyoti Zalkikar, Ph.D. Team Leader

Richard Chen, Ph.D., Biometrics Reviewer

Office of Medical Policy

Division of Drug Marketing, Advertising and Communications

Sean Bradley, Pharm.D.

Sponsor Attendees

Global Regulatory Affairs CMC:

Dr. Krishnan Viswanadhan, Regulatory

Dr. Cindy Dinella, Regulatory

Ms. Lisa Luther, Regulatory

Dr. Bruno Osterwalder, Clinical Science

Dr. Chris Dougherty, Clinical Science

Dr. Uli Beyer, Statistics

Dr. Philippe Van der Auwera, Life Cycle Leader

Mr. Chrys Kokino, US Business Operations

Dr. Delphine Oguey, Clinical Science

Dr. Patricia Erhard, Clinical Science

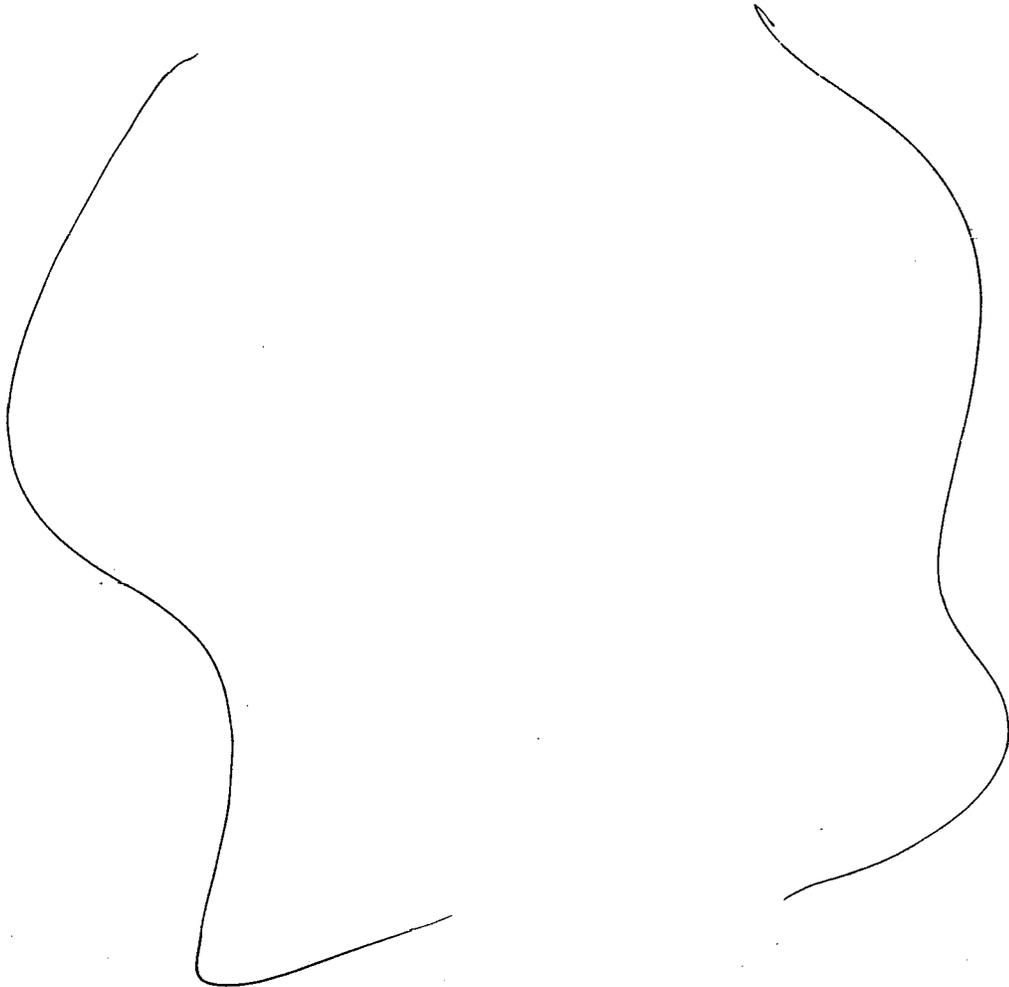
Kinnari Patel, Regulatory

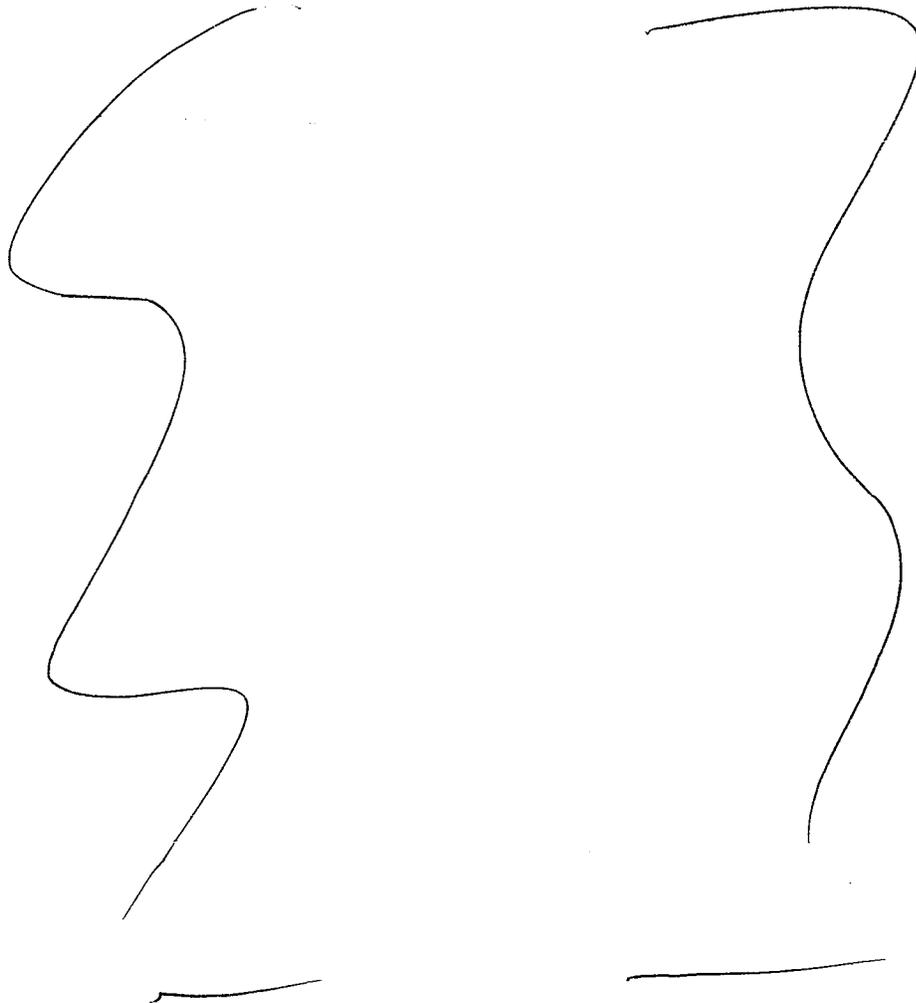
1.0 BACKGROUND

- Hoffman La-Roche submitted a Biologic License Application (BLA) on April 18, 2006 to support the use of Mircera for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and not on dialysis. Roche submitted a major amendment to their application on December 4, 2006. Roche's application was issued a complete response (CR) letter on May 18, 2007. On September 13, 2007, Roche resubmitted the Mircera application which was classified as a class 1 resubmission.
- Roche requested this Type C meeting to discuss their response to items identified in the May 18, 2007 CR letter, labeling and proposed post marketing commitments (PMC) for Mircera.

2.0 DISCUSSION

Both Roche and FDA agreed to discuss the most current version of the draft FDA "working" label sent to Roche on October 10, 2007 to have a productive and efficient meeting. FDA asked Roche to go through the label and provide FDA any feedback and





3.0 ISSUES REQUIRING FURTHER DISCUSSION

- Labeling
- Immunogenicity

4.0 ACTION ITEMS

- Roche to propose language that will address cancer use to address off-label use
- Roche to provide an outline of all the changes including numbers in the label and the cancer proposals as soon as possible prior to FDA's next labeling meeting to be held on October 18, 2007.
- Roche to submit all the European labels to the review division.

Moore, Florence O

From: Moore, Florence O
Sent: Monday, October 22, 2007 5:33 PM
To: 'Viswanadhan, Krishnan'
Subject: RE: PMCs

Thanks Krishnan. How many manufacturing sites /facility do you have for Mircera?

Florence

From: Viswanadhan, Krishnan [mailto:krishnan.viswanadhan@roche.com]
Sent: Monday, October 22, 2007 4:38 PM
To: Moore, Florence O
Subject: RE: PMCs

Hi Florence,

As requested, here is the copy of the cover letter in Word with the post approval commitments on the clinical side. I will follow-up with Susan Batcha to see what if any post approval commitments was discussed and agreed on the CMC side with Dr. Pluznik.

Kind Regards,
Krishnan

Krishnan Viswanadhan, Pharm.D.

Hoffmann-La Roche Pharmaceuticals

Pharma Development Regulatory

340 Kingsland Street

Nutley, NJ 07110

Telephone: (973)235-6241

Fax: (973)562-3700

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From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Monday, October 22, 2007 4:04 PM
To: Viswanadhan, Krishnan {PDR~Nutley}
Subject: PMCs

Hi Krishnan,

As discuss please send all CMC PMC proposals in word doc as well.

10/29/2007

Thanks,
Florence

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

*Tel: 301-796-1423
Fax: 301-796-9849*

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6 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-4

Record of Telephone Conversation

BLA: 125164

Today's date: October 11, 2006

Speakers: Kathy Robie Suh, John Lee, Dwaine Rieves--all for FDA
Krishnan Viswanadhan and others for Roche

Phone: 973-235-6241

FDA called Roche and informed them that FDA anticipates presentation of the BLA at an April 17 or 18 meeting of the Cardio-Renal Drugs Advisory Committee. FDA noted that Roche would be supplied with more logistical information once that information is available. FDA also informed Roche of a tentative internal FDA regulatory briefing that was primarily for informational purposes for CDER management. Roche asked multiple questions regarding the review findings and FDA reiterated that the review is ongoing. When Roche persisted in questions, FDA emphasized that repetitive questioning was not useful and FDA encouraged the sponsor to pursue constructive dialogue with the agency. FDA reiterated that results of the review would be provided to Roche as soon as the review was completed.

10 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 5



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

SEP 26 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 received your September 13, 2007 resubmission to your biologics license application for Mircera on September 14, 2007.

The resubmission contains additional clinical information that you submitted in response to our May 18, 2007 complete response letter.

We consider this a complete, class 1 response to our action letter. Therefore, the user fee goal date is November 14, 2007.

To further assist us in our review of the application in a timely manner, please provide the following additional information by October 7, 2007.

1. Provide the following additional analyses about maximum Mircera dose considerations.
 - a. For Mircera and each reference agent, please provide tables and figures which support the analyses specified in Attachment, items I-A and I-B.
 - b. Based on these analyses, please comment if a maximum dose should be specified for Mircera, above which the risk of an important clinical adverse event sharply rises. If the analyses show that the rise in adverse event risk is gradual without a sharp break, please comment if a maximum dose should still be specified, above which the risk is "considered to be clinically unacceptable."
 - c. Please comment if the maximum doses identified for each of the three ESAs (epoetin alfa, darbepoetin alfa, Mircera) as defined above correlate with the same achieved hemoglobin level for the three agents, and therefore a maximum dose and a single common target hemoglobin should be specified for each of the three agents.

- d. Please comment if the maximum doses identified for each of the three ESAs as defined above correlate with different achieved hemoglobin levels for the three agents, and therefore a maximum dose and different target hemoglobin should be specified for each of the three agents.
2. Regarding the use of transfusions, perform analyses to identify a threshold hemoglobin value below which the risk of transfusion importantly increases. Specifically, provide an analysis of transfusion use plotted versus the hemoglobin level, as specified in Attachment, item II. If the analyses disclose important considerations for Mircera labeling, submit the labeling modification.
3. For clarification of the contents or format for these analyses, please contact Dr. John Lee at 301-796-1396.

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

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, at (301) 796-2090.

Sincerely,



Rafel Dwaine Rieves, M.D.
Acting Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment

I. Maximum Dose

A. Correction Studies (to explore relationship among dose, achieved hemoglobin, and adverse events)

For the phase 3 correction studies, provide the following table for each study and for each agent used (2 studies x 2 agents per study = 4 tables):

| Month | Hb | Dose | AE1 | AE2 | AE3 | AE4 |
|-------|----|------|-----|-----|-----|-----|
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |

Define column headings as follows:

- Month = study month (e.g., Month 1 = beginning of study through end of first month of treatment)
- Hb = mean of all achieved hemoglobins during a given month
- Dose = mean of all doses given during a given month, NORMALIZED as total dose/kg/week
- AE1 = proportion of PATIENTS experiencing any of the following adverse events during a given month, as a fraction of all patients treated during that month: death, myocardial infarction, stroke, congestive heart failure.
- AE2 = proportion of patient-weeks that contain ANY of the following ADVERSE EVENTS during a given month, as a fraction of all patient-weeks for that month: death, myocardial infarction, stroke, congestive heart failure. An event occurring in one month and persisting into the next month should NOT be counted as a second event for the second month.
- AE3 = proportion of PATIENTS experiencing any serious adverse event during a given month, as a fraction of all patients treated during that month.
- AE4 = proportion of patient-weeks that contain a SERIOUS ADVERSE EVENT during a given month, as a fraction of all patient-weeks for that month.

For each cell, provide the following:

- The value as specified by the cell's column and row headings.
- For hemoglobin and dose, the sample size n contributing to the calculation of the cell value.
- For proportions of patients or patient-weeks, the numerator and denominator values used to calculate the proportions.
- For each of the four tables generated as specified above, construct figures to graphically illustrate the following potential correlations:
- Study month (x-axis) versus mean achieved hemoglobin during that month (y-axis). Although this figure has been previously provided in the BLA, provide this figure again alongside other figures specified below.

- Study month (x-axis) versus mean of doses given that month, normalized as dose/kg/week (y-axis). Although this figure has been previously provided in the BLA, provide this figure again alongside other figures specified below.
- Mean achieved hemoglobin (y-axis) versus mean normalized dose (x-axis)
- Mean achieved hemoglobin (x-axis) versus AE1, AE2, AE3, and AE4 (y-axis). Provide four separate figures, one for each specific definition of adverse event.
- Mean normalized dose (x-axis) versus AE1, AE2, AE3, and AE4 (y-axis). Provide four separate figures, one for each specific definition of adverse event.

B. Maintenance Studies (to explore relationship between responsiveness and adverse events)
 For phase 3 hemoglobin maintenance studies, provide the following table for each study and for each agent (4 studies x 2 agents per study = 8 tables):

| DRL | Patients | Hb | Dose | AE1 | AE2 | AE3 | AE4 |
|-----|----------|----|------|-----|-----|-----|-----|
| 1 | | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | | | | | | | |
| 5 | | | | | | | |
| 6 | | | | | | | |
| 7 | | | | | | | |

Define column headings as follows:

- DRL = dose responsiveness level. To define the dose responsiveness level, divide the full range of normalized doses (dose/kg/week) observed throughout the entire study into 7 equally-spaced increments of normalized dose; dose responsiveness levels 1 through 7 represent successively higher categories of equal dose range span.
- Patients = proportion of patients exposed to the study medication at a dose level within a given DRL, as a fraction of all patients.
- Hb = mean of all achieved hemoglobins for a given DRL. Link a given dose with the nearest hemoglobin value obtained after administering the dose. If a dose was missed, incorporate the missed dose (value of 0) into the next two doses actually given in calculating a single normalized dose value for the three scheduled dose administrations.
- Dose = mean of all doses for a given DRL (normalized as total dose/kg/week).
- AE1 = proportion of PATIENTS experiencing any of the following adverse events in association with a given DRL, as a fraction of all patients exposed to that DRL: death, myocardial infarction, stroke, and congestive heart failure. Link a given event with the nearest dose given before the event.
- AE2 = proportion of patient-weeks that contain ANY of the following ADVERSE EVENTS occurring in association with a given DRL, as a fraction of all patient-weeks exposed to that DRL: death, myocardial infarction, stroke, and congestive heart failure. Link a given event with the nearest dose given before the event.

- AE3 = proportion of PATIENTS experiencing any serious adverse event in association with a given DRL, as a fraction of all patients exposed to that DRL. Link a given event with the nearest dose given before the event.
- AE4 = proportion of patient-weeks that contain a SERIOUS ADVERSE EVENT in association with a given DRL, as a fraction of all patient-weeks exposed to that DRL. Link a given event with the nearest dose given before the event.

For each cell, provide the following:

- The value as specified by the cell's column and row headings.
- For hemoglobin and dose, the sample size n contributing to the calculation of the cell value.
- For proportions of patients or patient-weeks, the actual numerator and denominator values used to calculate the proportions.

For each of the 8 tables generated as specified above, construct figures to graphically illustrate the following potential correlations:

- DRL (x-axis) versus proportions of patients in the DRL category (y-axis).
- DRL (x-axis) versus mean achieved hemoglobin for that DRL (y-axis).
- DRL (x-axis) versus AE1, AE2, AE3, and AE4 (y-axis). Provide four separate figures, one for each specific definition of adverse event.

II. Transfusion Requirement (to assess efficacy in reducing the need for transfusion)

For phase 3 correction studies, provide the following table for each study and for each agent (2 studies x 2 agents per study = 4 tables):

| Month | Hb | Patients | Transfusions | Units |
|-------|----|----------|--------------|-------|
| 1 | | | | |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | | | | |
| 6 | | | | |
| 7 | | | | |

Please define column headings as follows:

- Month = study month (e.g., Month 1 = beginning of study through end of first month of treatment)
- Hb = mean of all achieved hemoglobins during a given month
- Patients = proportion of patients who received a red blood cell transfusion during a given month, as a fraction of all patients enrolled in the study during that month.

- Transfusions = number of instances of red blood cell transfusion during a given month. Define one "instance" to include any number of units given to a patient within 24 hours of the first unit.
- Units = number of units of red blood cells transfused during a given month.

For each cell, provide the following:

- The value as specified by the cell's column and row headings.
- For hemoglobin and dose, the sample size n contributing to the calculation of the cell value.
- For proportion of patients, the numerator and denominator values used to calculate the proportion.

For each of the four tables generated as specified above, construct figures to graphically illustrate the following potential correlations:

- Study month (x-axis) versus proportion of patients who received a red blood cell transfusion during that month (y-axis).
- Study month (x-axis) versus number of transfusions given during that month (y-axis).
- Study month (x-axis) versus number of units given during that month (y-axis).
- Monthly mean hemoglobin (x-axis) versus proportion of patients who received a red blood cell transfusion during that month (y-axis).
- Monthly mean hemoglobin (x-axis) versus number of transfusions given during that month (y-axis).
- Monthly mean hemoglobin (x-axis) versus number of units given during that month (y-axis).



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0 and IND 10158

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

SEP 26 2007

Dear Dr. Viswanadhan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We also refer to the teleconference held on August 30, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely yours,

{See appended electronic signature page}

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type A

Meeting Category: Safety Data Assessment

Meeting Date and Time: August 30, 2007

Meeting Location: CDER WO 2376 Conf Room Bldg 22

Application Number: STN 125164/0 and IND 10158

Product Name: Pegylated Erythropoietin beta (human, recombinant, CHO cells, Hoffmann La-Roche)

Received Briefing Package: July 27, 2007

Sponsor Name: Hoffman La-Roche

Meeting Requestor: Krishnan Viswanadhan, Pharm.D.

Meeting Chair: Rafel Rieves, M.D.

Meeting Recorder: Florence Moore, M.S.

Meeting Attendees:

FDA Attendees

Office of Oncology Drug Products

Division of Medical Imaging and Hematology Products

Rafel (Dwayne) Rieves, M.D., Acting Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader

John Lee, M.D., Medical Reviewer

Florence Moore M.S., Regulatory Health Project Manager

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader

Office of Biostatistics

Division of Biometrics V

Jyoti Zalkikar, Ph.D. Biostatistics Team Leader

Richard Chen, Ph.D. Biostatistics Reviewer

Sponsor Attendees

Global Regulatory Affairs CMC:

Dr. Krishnan Viswanadhan, Director, Regulatory Affairs

Ms. Lisa Luther, Senior Director, Regulatory Affairs

Dr. Cindy Dinella, Vice President, Regulatory Affairs

Dr. Chris Dougherty, Clinical Science Leader

Dr. Philippe Van der Auwera, Life Cycle Leader

Dr. Julianne Essig, Drug Safety

Dr. Bruno Osterwalder, Clinical Science

Dr. Uli Beyer, Statistics

1.0 BACKGROUND

- Hoffman La-Roche submitted a Biologic License Application (BLA) on April 18, 2006 to support the use of Mircera for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and not on dialysis. Roche submitted a major amendment to their application on December 4, 2006, which included a September 1, 2006 safety update report, a cardiovascular mortality adjudication report, datasets, case report forms and an updated labeling. Roche's application was issued a complete response (CR) letter on May 18, 2007 due to the safety concerns that has come up with the class of erythropoiesis-stimulating agents (ESA).
- Roche requested this Type A meeting under their IND 10158 to discuss the proposed post approval commitment study and to gain FDA's perspectives on the proposed study.

2.0 DISCUSSION

1.



Roche has developed a major proposal synopsis for further discussion with FDA.

FDA Response:

The discussions from the upcoming Advisory Committee may importantly impact the design of your post-marketing commitment study and we cannot provide definitive comment regarding your proposal until we have reviewed and considered the Committee's advice. Nevertheless, we regard an open label design as a reasonable proposal for a study that uses objective, robust safety endpoints. If you intend to measure "quality of life" (patient reported outcomes, PRO) as an important study objective, the study should use a double-blinded design.

2. *Roche submitted to FDA a request for Special Protocol Assessment of protocol, NH20052, a registration study to support once monthly use of RO0503821 in the correction setting in September 2006 (S-251) and FDA provided comments on November 9, 2006. Protocol NH20052 was amended on June 28, 2007 to address all comments from FDA regarding protocol deficiencies following a SPA review. As part of the SPA comments, FDA requested that the study be revised to use a double blind design and noted that this was an important consideration in the context of accumulating safety data regarding the use of ESAs and the potential for an open label study to result in bias in the detection of safety. Roche revised the study from open label to double blind since FDA noted that this was one of the elements that must be addressed to obtain concurrence under the SPA. We are requesting FDA to reconsider their feedback regarding blinding in light of the recent acceptance of open label trials for the Hematide phase III program as well as the overall safety database accumulated from the 10 phase II and III trials conducted to evaluate the safety of RO0503821. In addition, Roche has encountered*

Roche looks forward to hearing from FDA as soon as possible on the acceptance of modifying NH20052 to an open label study.

Roche requests FDA to reconsider their feedback regarding blinding on the following grounds:

*i. **Fairness***

FDA appears to have accepted the adequacy of open label trials for the Phase 3 registration program for Hematide as noted in recent Affymax press release (Attachment 1). Specifically, the two correction studies for Hematide are open-label trials in non-dialysis patients designed to evaluate the safety and efficacy of Hematide once monthly compared to Darbepoetin in correcting and maintaining hemoglobin levels.

*ii. **ESA development Programs including Mircera Utilized Open-Label Trials Without Bias***

Roche has conducted 4 and 6 Phase 3 open label trials to evaluate and establish the safety and efficacy of RO0503821 in the treatment of anemia associated with chronic kidney disease, involving 1789 patients. In light of the large clinical

experience and safety database which has demonstrated the safety of RO0503821, Roche does not see the benefit of blinding in the correction study, NH2005.

The primary efficacy endpoints are based on an objective to note the ethical considerations and the need to administer many placebo injections to maintain a blind environment due to the differences in the administration frequency.

iii. Feasibility of Double-Blind Trials



In light of the points noted above, Roche intends to amend protocol NH20052 to an open-label trial and proceed unless FDA responds differently within 30 days.

FDA Response:

We continue to support the use of a double-blinded study design. However, we do not object to your proposed alteration to an open label study design. Ultimately, the study results will determine the usefulness of the data to support a labeling alteration. In general, compared to open label studies, double blinded studies provide more persuasive data to support labeling alterations.

Additional Discussions

Roche asked FDA to give them an idea of what the FDA envisions the outcome of the CRDAC meeting would be and how FDA would move forward with the Mircera application. FDA stated that we could not prospectively give Roche what we envision the outcome of the meeting would be and that we are awaiting the discussions from the meeting before we can discuss future studies and commitments.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- PMC studies that would be discussed at the September 11, 2007 CRDAC meeting.

4.0 ACTION ITEMS

N/A

5.0 ATTACHMENTS AND HANDOUTS

N/A

Linked Applications

Sponsor Name

Drug Name

IND 10158

HOFFMANN-LA ROCHE
INC

Pegylated Erythropoietin beta (human,
recombinant, CHO cells, Hoffmann-
LaRoche)

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

/s/

FLORENCE O MOORE
09/26/2007

Moore, Florence O

From: Moore, Florence O
Sent: Monday, September 24, 2007 9:57 AM
To: 'Viswanadhan, Krishnan'
Subject: Immunogenicity info from Roche

Good morning Krishnan,

A while back we requested Roche for information regarding the level of drug on board when samples were tested for the presences of Abs. Can you tell me in which submission your response to our request was in?

Thanks,
Florence

Moore, Florence O

From: Moore, Florence O
Sent: Thursday, August 30, 2007 10:56 AM
To: 'Viswanadhan, Krishnan'
Subject: NH20052

Krishnan,

When did you submit the NH20052 study. Please give me the dates and sequence number.

Thanks,

Florence O. Moore, M.S.
Regulatory Health Project Manager
FDA/CDER/OODP/DMIHP
Building #22/Room 2381
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone 301-796-1423
Fax 301-796-9849



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

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

AUG 24 2007

Dear Dr. Viswanadhan:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We also refer to the teleconference held on July 27, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2050.

Sincerely yours,

A handwritten signature in black ink, appearing to read "F. O. Moore".

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type C

Meeting Category: Chemistry, Manufacturing and Control

Meeting Date and Time: July 27, 2007

Meeting Location: CDER White Oak Bldg 22 Conference Room 2376
and CDER, OBP, OPS, DTP Conference Room, Bldg. 29A Room
2D-20, NIH Campus

Application Number: STN 125164/0

Product Name: Pegylated Erythropoietin beta (human, recombinant, CHO cells,
Hoffmann La-Roche)

Received Briefing Package: N/A

Sponsor Name: Hoffman La-Roche

Meeting Requestor: Susan Batcha

Meeting Chair: Dov Pluznik, Ph.D.

Meeting Recorder: Florence Moore, M.S.

Meeting Attendees:

FDA Attendees

Office of Biotechnology Products
Division of Therapeutic Products (DTP)
Barry Cherney, Ph.D., Deputy Director,
Dov Pluznik, Ph.D., Product Quality Reviewer
Ingrid Markovic Ph.D., Product Quality Reviewer

Office of Oncology Drug Products

Division of Medical Imaging and Hematology Products

John Lee, M.D., Medical Officer

Florence Moore, M.S. Regulatory Project Manage

Sponsor Attendees

Dr. Christof Finkler Analytics/Quality Control Drug Product—Basel

Dr. Bernd Moritz Analytics/Quality Control Drug Product—Basel

Dr. Christian Siegmund Galenical Manufacturing—Basel

Dr. Harald Haug Head of Quality Control Drug Substance—Penzberg

Dr. Christoph Lindenthal Analytics/Quality Control Drug Substance—Penzberg

Dr. Markus Dembowski Research Analytics Drug Substance—Penzberg

Dr. Alexander Wrba Local Technical Leader EPO Starting Material
—Penzberg

Dr. Hermann Tebbe Local Technical Leader EPO Starting Material
—Penzberg

Dr. Klaus Reichert Local Technical Leader Drug Substance Manufacturing—
Penzberg

Dr. Wulf Pahlke Quality Analytics/Bioassay—Mannheim

Mr. Jean-Pierre Buch Global Technical Team Leader

Ms. Susan Batcha Technical US Regulatory Affairs

Dr. Krishnan Viswanadhan Global Regulatory Leader/US Regulatory Affairs

Dr. Richard Steinbach Group Director/Technical US Regulatory Affairs

Dr. Cynthia Dinella Vice President/US Regulatory Affairs

Dr. Lisa Luther Group Leader/US Regulatory Affairs

Meeting Summary

The purpose of this t-con was to address and clarify the following issues:

- Discuss CMC response to the CR letter provided to DTO by e-mail on June 15 and June 22. Identify postapproval commitments
- Discuss expectations for Roche response to pooling questions for EPO starting material, _____ and Drug Substance as requested in FDA fax list of questions from May 8, 2007 (Questions 4, 6, and 8)
- Clarify if responses provided by Roche in Amendment #39 for May 8 fax questions 4 to 10 (other than the pooling questions) have been accepted or require further information data
- Status update for final study reports of leachable and extractable studies for pre-filled syringe container closure
- Clarify if there are any open issues for review of carton and container labeling from the CMC perspective

7 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-6



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

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

AUG 23 2007

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application (BLA) submitted under Section 351 of the Public Health Service Act.

We also refer to your August 13, 2007 correspondence requesting a meeting to discuss your labeling; post marketing commitments based on the recommendations from September 11, 2007 Cardio-Renal Advisory Committee meeting, any outstanding questions from the May 18, 2007 complete letter and timelines for your BLA. We consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: October 11, 2007

Time: 12:00 PM -1:30 PM (Eastern Time)

Location: CDER White Oak Building 22

CDER Participants:

Rafel Rieves, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader
John Lee, M.D., Clinical Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Jang-Ike Lee, Ph.D., Clinical Pharmacology Reviewer
Yanli, Ouyang, Ph.D., Preclinical Reviewer
Jyoti Zalikikar, Ph.D., Biometrics Team Leader
Richard Chen, Ph.D., Biometrics Reviewer
Pravin Jadhav, Ph.D., Clinical Pharmacology Reviewer
Florence Moore, M.S., Regulatory Health Project Manager (DMIHP)

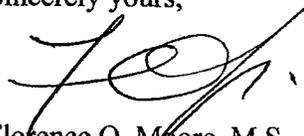
CDER Optional Participants:

Richard Pázdur, M.D., Director (OODP)
Karen Weiss, M.D., Deputy Director (OODP)
Barry Cherney, Ph.D. Deputy Director (DTP)
Emily Shacter, Ph.D. CMC Laboratory Chief (DTP)

Dov Pluznik, Ph.D. CMC Reviewer (DTP)
Susan Kirshner, Ph.D. CMC Reviewer (DTP)
Ingrid Markovic, Ph.D. CMC Reviewer (DTP)
Serge Beaucage, Ph.D. CMC Reviewer (DTP)
Patricia Hughes, Ph.D., Facility Reviewer (DMPQ)
Mike Welch, Ph.D., Deputy Director (Biostatistics)
Sharon Mills, Reviewer (SEALD)
Iris Masucci, Reviewer (SEALD)
Sean Bradley, Pharm.D., Reviewer (DDMAC)

If you have any questions, call me at (301) 301-796-2050.

Sincerely yours,



Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125164/0

SEP 04 2007

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

Dear Dr. Viswanadhan,

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Mircera (Pegzerepoetin).

The use of Mircera will necessitate special attention to dosage and patient monitoring considerations as well as considerations of the overall risks and benefits of the product in specific clinical situations. As summarized in the boxed warning other erythropoiesis-stimulating agents (ESAs), these products pose a serious and significant public health concern relating to:

- Increased risk for death and for serious cardiovascular events in certain patients;
- A shortened time to tumor progression, increased overall mortality and increased mortality attributed to disease progression when ESAs were used among certain patients with cancer;
- Increased risk for deep vein thrombosis among certain patients receiving ESAs pre-operatively for reduction of allogeneic red blood cell transfusions.

These concerns require development and distribution of a Medication Guide under 21 CFR 208 in order to help prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

Submit your proposed Medication Guide by October 1, 2007. Once Mircera is approved, under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Mircera. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Mircera that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug (e.g., bolded statement "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide)." The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc).

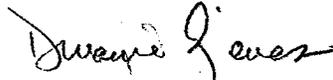
Include content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

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

If you have any questions, please contact the Regulatory Project Manager, Florence Moore, M.S., at (301) 796-2050.

Sincerely,

A handwritten signature in black ink, appearing to read "Dwaine Rieves". The signature is written in a cursive style with a large initial "D".

Rafel (Dwaine) Rieves, M.D.
Acting Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN BLA 125164/0

JUN 14 2007

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

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application (BLA) for Mircera (Pegzerepoetin alfa), submitted under Section 351 of the Public Health Service Act.

We also refer to our May 18, 2007 Complete Response letter and to your May 29, 2007 letter and to the June 11, 2007 and June 12, 2007 teleconferences between representatives of Hoffman La-Roche and FDA. We acknowledge your intent to file a resubmission to address the deficiencies identified in our Complete Response letter.

We understand your desire for "timely completion of the Mircera review" following an FDA Advisory Committee meeting in early Fall 2007. Because we share this goal, we requested specific postmarketing commitment proposals and provided you with detailed preliminary comments on labeling. However, a meeting to discuss this application prior to considering input from the Advisory Committee is premature and would not serve a useful purpose. As explained in our Complete Response letter, we consider the discussion and recommendations of the upcoming Advisory Committee necessary in determining what information you should include in your resubmission (e.g. labeling, postmarketing study proposals, and data). Given the importance of this information to the further review of your application, we again recommend that you request a meeting with us to occur shortly after the Advisory Committee meeting and prior to your BLA resubmission. We believe the most efficient path for continued review and possible approval of Mircera is summarized as follows:

- Submission of postmarketing study proposals, as requested in our Complete Response letter, to your IND
- Fall 2007 Advisory Committee meeting
- Hoffman La-Roche meeting with FDA review division [if necessary] following the Advisory Committee meeting
- BLA resubmission

Regarding your plan to submit, over the subsequent months, portions of a Complete Response to our Complete Review letter of May 18, 2007: as you are aware, “a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.” It will not be possible to submit a complete response until after the Advisory Committee because information from the Advisory Committee may importantly impact the contents of your response to the May CR letter. We encourage you to thoroughly evaluate the discussions from that meeting when developing your response. However, we do invite you to submit your responses to questions 1a-1d of the May 18, 2007 CR letter in advance of the complete response.

With respect to your request for "agreement" regarding the classification of the response to the May 18, 2007 letter, we cannot make a decision on the classification of the resubmission until we have received the submission and the review team agrees that you have addressed all the issues.

Regarding the structure, timelines and your role for the September Advisory Committee, as discussed in the teleconferences, the focus of the meeting is 1) the safety of erythropoiesis-stimulating agents as a class; and 2) available data regarding “Quality of Life” claims. We do not intend to discuss the specific data regarding the safety and efficacy of Mircera. Therefore, if you wish to present your data at the Advisory Committee, you must inform us no later than June 18 so that we can make appropriate changes to the meeting agenda to incorporate a discussion of the specific data on the safety and efficacy of Mircera.

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,



Karen Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Moore, Florence O

From: Moore, Florence O
Sent: Monday, August 13, 2007 5:43 PM
To: 'Viswanadhan, Krishnan'
Subject: Mircera PMCs

Hi Krishnan,

Were the draft PMC sent officially to the BLA?

Thanks,
Florence

Florence O. Moore, M.S.
Regulatory Health Project Manager
FDA/CDER/ODDP/DMIHP
Building #22/Room 2381
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone 301-796-1423
Fax 301-796-9849

Moore, Florence O

From: Pluznik, Dov
Sent: Wednesday, August 01, 2007 2:03 PM
To: 'Batcha, Susan Ann'
Cc: Cherney, Barry; Moore, Florence O; Markovic, Ingrid; Rawls, Sheila
Subject: RE: BLA STN125164_FDA Teleconference July 27 regarding Roche responses to FDA CR letter
Follow Up Flag: Follow up
Flag Status: Red
Attachments: Carton.container label items.doc; Extractables & leachables comments.doc

Susan,

As agreed in our telecom of July 27, 2007, attached please find the questions and comments regarding leachables/extractables and carton/container labeling.



Dr. Dov Pluznik

From: Batcha, Susan Ann [mailto:susan_ann.batcha@roche.com]
Sent: Monday, July 30, 2007 11:35 AM
To: Pluznik, Dov
Subject: BLA STN125164_FDA Teleconference July 27 regarding Roche responses to FDA CR letter

Dear Dr. Pluznik,

At the above referenced teleconference, FDA stated that questions and comments regarding the leachable and extractable study reports for ~~_____~~ container closures and FDA CMC comments for carton and container labeling would be sent to Roche separately. As per our telephone conversation this morning, the FDA questions and comments may be sent to my e-mail address. I will then forward these to the appropriate team members.

Best regards,

Susan Batcha

Confidentiality Note: This message is intended for the use of the named recipient(s) only and may contain confidential and/or proprietary information. If you are not the intended recipient, please contact the sender and delete this message. Any unauthorized use of the information contained in this message is prohibited.

1 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 7

2 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

8

Moore, Florence O

From: Moore, Florence O
Sent: Tuesday, July 03, 2007 1:31 PM
To: 'Viswanadhan, Krishnan'
Subject: RE: Mircera BLA

Hi Krishnan,

I have tentatively scheduled the t-con for July 27, 2007; 1:30-2:30 PM (this might take only 30 minutes). However, I am waiting for the products reviewers to confirm. I will update you once I hear from them so you can provide a call in number.

Thanks,
Florence

From: Viswanadhan, Krishnan [mailto:krishnan.viswanadhan@roche.com]
Sent: Monday, July 02, 2007 10:07 AM
To: Moore, Florence O
Subject: Mircera BLA

Hi Florence:

I am emailing you to schedule a teleconference with the relevant participants from the CMC review team to get clarification on some of the questions in the Mircera complete response letter. Susan Batcha has been discussing with Dr. Pluznik and it was recommended that a teleconference with Dr. Pluznik and Dr. Cherney could occur either on July 30th or July 31st. I just wanted to follow up with you so that we can ensure that the teleconference date/time has been scheduled.

Thanks a lot as always. Hope you had a good vacation.

Kind Regards,
Krishnan



Our STN: BL 125164/0

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

JUN 30 2006

Dear Dr. Viswanadhan:

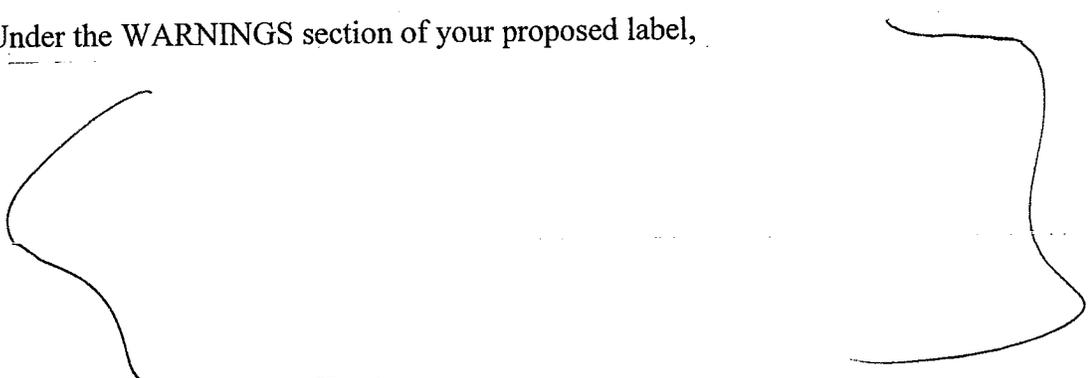
This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated April 18, 2006 for Pegserepoetin alfa to determine its acceptability for filing. Under 21 CFR 601.2(a) we filed your application June 1, 2006. The user fee goal date is February 17, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any substantive evaluation of the data submitted.

While conducting our filing review, we identified the following potential review issues:

Clinical:

1. Your safety data include nine cases of sudden deaths in the study agent arms versus none in the reference arms. This imbalance in sudden deaths raises concerns regarding your product's safety. Evaluation of reasons for and implication of this imbalance in the occurrence of sudden death will be an important area of focus during our review.
2. Under the WARNINGS section of your proposed label,



Please be aware that the lack of sufficient clinical data supporting your

proposed labeling will necessitate modifications in your proposed product label. Our preliminary review appears to indicate that your clinical data are very limited or insufficient to support the proposed product label's description of the target hemoglobin concentration and the limiting hemoglobin _____ We encourage you to consider submitting product labeling that has been revised to address our concerns regarding the target hemoglobin concentration and the hemoglobin monitoring plan. Alternatively, we suggest that you amend your BLA to clearly identify the clinical data supporting the safety of your proposed product label's description of the target hemoglobin concentration and the hemoglobin _____ and provide justification for the target hemoglobin proposed for the labeling.

Preclinical:

3. Neither GLP statement nor the statement justifying the non-compliance was provided for the studies outlined below which were used for supporting non-clinical safety. Please provide either a statement stating that the study was conducted in compliance with the GLP requirements set forth in 21 CFR Part 58 or a brief statement justifying the non-compliance, if the study was not conducted in compliance with such regulations for the following study reports:
 - 1015621 “ Ligand-Receptor Binding Study of RO0503821 (CERA) with Normal Human Tissues” (PAI Study No. IM946, HLR Study No. 08392)
 - 1019698 “ The Influence of RO0503821 on Proliferation in Established Erythropoietin Receptor Positive and Negative Cell Lines”
 - 1004870 -1017 Ro 50-3821/000 “ A single-dose intravenous and subcutaneous injection site local tolerability study in rabbits” (study no. 07441).
 - 1004874 – 1018 Ro 50-3821/000 (PEG-EPO) “ A single dose subcutaneous injection site local tolerability study in rabbits” (study no. 07452).
 - 1005338 – 1019 Ro 50-3821/000 “A single dose intravenous and subcutaneous injection site tolerability study in rabbits” (study no. 07594).

4. The following study design issues were identified and may significantly affect study result interpretation and comprehensive safety evaluation:
 - Validation study for the measurement method of anti-RO0503821 antibodies in dog serum was not provided.
 - Only subcutaneous administration was used in the teratology and toxicokinetic study of Ro 50-3821/000 in rabbits despite that both subcutaneous and

intravenous administration will be used in clinical practice. Furthermore, no comparative (SC vs. IV) PK data were available for rabbits.

- Anti-RO0503821 antibodies measurements were not conducted for teratology studies.
5. Pending Chemistry Manufacturing Control (CMC) issues identified are still under discussion and will be forwarded to you in a separate letter.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

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

Effective August 29, 2005, the new address for all submissions to this application is:

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

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,



George Q. Mills, M.D., M.B.A.

Director

Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF ONCOLOGY DRUG PRODUCTS
DIVISION OF BIOLOGIC ONCOLOGY PRODUCTS

White Oak Office Complex – Building 22
10903 New Hampshire Avenue
Sliver Spring, Maryland 20993
FAX #: 301-796-9849

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 34 (Including Cover Page)

FAX TO: Krishnan Viswanadha

Facsimile Telephone No. 973-562-3700 Voice Telephone No. 973-235-6241

FROM: Florence Moore

ALL FOR FM 6/30/06

Facsimile Telephone No. 301-796-9849 Voice Telephone No. 301-796-2050

DATE: 6/30/06

TIME: 3 PM

MESSAGE: _____

Please call to confirm that you have received this fax. Thanks.

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Due Date 6/30/06

BLA Letter Routing Slip

STN # 125164/10

Letter Type DT

FINAL ROUTING AND SIGNATURES

TYPIST

/date final typed

J Moore 6/29/06

RPM

/date file box signed

J Moore 6/29/06

CPMS

/date file box signed

[Signature]

CDER DMPQ BRANCH

CHIEF

/date file box signed

CDER DMPQ

DIRECTOR

/date file box signed

COMMITTEE CHAIR

/date file box signed

DBOP/PRODUCT DIRECTOR

/date file box signed

CODE DIRECTOR

/date file box signed

[Signature] 6/30/06

DBOP TYPIST

/date sent to sponsor

J Moore 6/30/06

Milestone Entered

N:\townsend\forms\BL Aroute.doc
10-24-05

7/3/06

Due Date 6/30/06

BLA Letter Routing Slip

STN # 125164/0

Letter Type DL

RPM

/date drafted

F. Moore 6/1/06

CPMS

/date draft initialed

TYPIST

/date final draft typed

F. Moore 6/28/06

email sent to:

- | | | |
|----------------------------|--------------------|-----------|
| <u>NA G Mills</u> | <u>S Kurshner</u> | <u>NC</u> |
| <u>NA R Reeves</u> | <u>J. Zalkovsk</u> | <u>NC</u> |
| <u>6/28/06 K Robie Est</u> | <u>R. Chen</u> | <u>NC</u> |
| <u>6/28/06 J Lee</u> | <u>B. Upreti</u> | <u>NC</u> |
| <u>6/28/06 A Kanyon</u> | <u>P. Hughes</u> | |
| <u>NA Y Ouyang</u> | <u>S. Yu</u> | <u>NC</u> |
| <u>K. Tang</u> | <u>J. Rouire</u> | |
| <u>A Kacubs</u> | <u>H. Zhao</u> | <u>NC</u> |
| <u>F. Moore</u> | <u>J. Lee</u> | <u>NC</u> |
| <u>6/28/06 E. Shacter</u> | <u>S. Bradley</u> | |
| <u>D. Puznik</u> | | |
| <u>J. Markovic</u> | | |
| <u>S. Bearce</u> | | |

3:24 pm 6/28/06
/date & time

RPM

/date response(s) rec'd (or no resp), final draft

F. Moore 6/29/06

TYPIST

/date final draft sent to DBOP Director & R. Reeves, K. Robie Est, A. Kanyon
Name of Signatory Director(s)

FINAL DRAFT CONCURRENCE

CONCURRENCE DATE

6/29/06



Our STN: BL 125164/0

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

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application (BLA) for Mircera (Pegzerepoetin alfa), submitted under Section 351 of the Public Health Service Act.

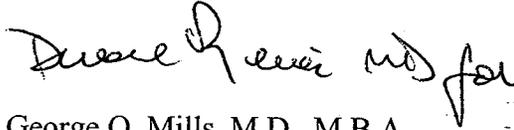
We also refer to your December 4, 2006 major amendment submission to your application. We have the following comments and information request:

1. The amendment does not appear to contain a summary of the specific site identification information necessary to readily correlate sites with deaths. Please provide three tables (data through previous April cutoff, interim data, all data through the new September cutoff), each listing the following information for all deaths:
 - study site number
 - study site location
 - description of study site (size and type of medical facility)
 - which study was performed at that site (phase 2 or phase 3 study identification number)
 - total number of patients enrolled at that site (for each study, if more than one study was performed at that site)
 - total number of patients with adverse events reported at that site
 - total number of patients with serious adverse events at that site
 - total number of deaths at that site

We request that you respond to item 1 as soon as possible and no later than December 20, 2006.

If you have any questions, please contact the Regulatory Project Manager,
Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,

A handwritten signature in black ink, appearing to read "George Q. Mills M.D. M.B.A.", written in a cursive style.

George Q. Mills, M.D., M.B.A.

Director

Division of Medical Imaging and Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Deficiencies (DI)

SS Data Check:

- **Communication**
- **Milestone: Confirm Filing Action Entry & Close Date**
- **If applicable – Confirm Deficiencies Identified Entry & Close Date**

cc: DMIHP-G. Mills, R. Rieves, K. Robie Suh, J. Lee, A. Lanionu, Y. Ouyang, F. Moore.

DTP: A. Rosenberg, E. Shacter, D. Pluznik, I. Markovic, S. Beaucage, S. Kirshner

DCP- H. Zhao, J. Ik Lee

DBV- J. Zalkikar, R. Chen

OODP- R. Pazdur, K. Weiss

HFD-005/Mike Jones

HFD-40/Office of Medical Policy/R. Temple

HFD-123/OBP Director/Keith Webber

HFD-320/DMPQ Director/ Nick Buhay

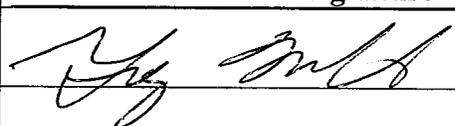
HFD-328/B Uratani

DRMP BLA file (hard copy)

HFD-020/ Immediate Office (hard copy)

History: F. Moore 6/1/06; F. Moore 6/29/06

File Name: S:\BLA\Letters\Filing\125164\0.DI.doc

| Office | Name/Signature | Date |
|------------|---|---------|
| 000P/DMINR |  | 6/30/06 |
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| | | |



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125164/0

Name of Drug: Methoxy polyethylene glycol-epoetin beta

Sponsor: Hoffmann-LaRoche, Inc.

Material Reviewed: Mircera® (Methoxy polyethylene glycol-epoetin beta) Carton and Container Labels

Submission Date: February 9, 2007

Receipt Date: February 12, 2007

Background:

Hoffman-LaRoche, Inc. has submitted a Biologic License Application (BLA) for the treatment of anemia associated with chronic kidney disease (CKD), including patients on dialysis and not on dialysis. Draft carton and container labels were re-submitted on February 9, 2007.

Labels Reviewed:

Mircera® (Methoxy polyethylene glycol-epoetin beta) Carton Label

Mircera® (Methoxy polyethylene glycol-epoetin beta) Container Label

Review

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name of the product – Methoxypolyethylene glycol epoetin beta

5 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-9

Moore, Florence O

From: Moore, Florence O
Sent: Wednesday, June 20, 2007 3:58 PM
To: 'Viswanadhan, Krishnan'
Subject: RE: Message from 9732355000

Hi Krishnan

I got your message. 21 CFR 201.57 (d)(6): Under format requirements: "The letter requirement height or type size for all labeling information headings and subheadings set forth in paragraph (a), (b), and (c) of this section must be a minimum of 8 points....."

Regarding the carton label you might get the response after the resubmission. I've been on the CMC folks to give me comments, but I haven't received any yet. I will get you comments as soon as I get them from the reviewers.

Regards,
Florence

From: Unity Messaging System - FDAOIP14
Sent: Wednesday, June 20, 2007 2:50 PM
To: Moore, Florence O
Subject: Message from 9732355000

<< File: VoiceMessage >>

Moore, Florence O

From: Moore, Florence O
Sent: Tuesday, June 19, 2007 3:43 PM
To: 'Viswanadhan, Krishnan'
Subject: Mircera PLR

Hi Krishnan,

Some of the font in the PLR you submitted is 8 point and others are 12. They all have to be 8 point font. I've been playing around with it but it changes the format of the entire label. Please send in one with the correct font asap.

Thanks,
Florence

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

*Tel: 301-796-1423
Fax: 301-796-9849*

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Moore, Florence O

From: Moore, Florence O
Sent: Monday, June 18, 2007 11:18 AM
To: 'Viswanadhan, Krishnan'
Subject: RE: Mircera BLA 125164/0 - Question on Safety Update

Hi Krishnan:

We do need a safety update. Please provide an updated, interim summary of the important safety findings from studies of the product, based upon findings from the date of the previously reported safety update.

Regards,

*Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903*

*Tel: 301-796-2050
Fax: 301-796-9849*

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From: Viswanadhan, Krishnan [mailto:krishnan.viswanadhan@roche.com]
Sent: Monday, June 18, 2007 11:05 AM
To: Moore, Florence O
Subject: Mircera BLA 125164/0 - Question on Safety Update

Hi Florence:

We wanted to get clarification regarding the need for a safety update for Mircera as part of the responses to the CR letter.

As you are aware, the complete response letter dated May 18, 2007, does not indicate any need to provide a safety update. Therefore, our assumption is that there is no need to provide a safety update as part of the responses to the CR letter. We wanted to confirm with you that a safety update is not needed for our

10/29/2007

resubmission? Can you please confirm?

Kind Regards,
Krishnan



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN BLA 125164/0

JUN 14 2007

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

Dear Dr. Viswanadhan:

This letter is in regard to your biologics license application (BLA) for Mircera (Pegzerepoetin alfa), submitted under Section 351 of the Public Health Service Act.

We also refer to our May 18, 2007 Complete Response letter and to your May 29, 2007 letter and to the June 11, 2007 and June 12, 2007 teleconferences between representatives of Hoffman La-Roche and FDA. We acknowledge your intent to file a resubmission to address the deficiencies identified in our Complete Response letter.

We understand your desire for "timely completion of the Mircera review" following an FDA Advisory Committee meeting in early Fall 2007. Because we share this goal, we requested specific postmarketing commitment proposals and provided you with detailed preliminary comments on labeling. However, a meeting to discuss this application prior to considering input from the Advisory Committee is premature and would not serve a useful purpose. As explained in our Complete Response letter, we consider the discussion and recommendations of the upcoming Advisory Committee necessary in determining what information you should include in your resubmission (e.g. labeling, postmarketing study proposals, and data). Given the importance of this information to the further review of your application, we again recommend that you request a meeting with us to occur shortly after the Advisory Committee meeting and prior to your BLA resubmission. We believe the most efficient path for continued review and possible approval of Mircera is summarized as follows:

- Submission of postmarketing study proposals, as requested in our Complete Response letter, to your IND
- Fall 2007 Advisory Committee meeting
- Hoffman La-Roche meeting with FDA review division [if necessary] following the Advisory Committee meeting
- BLA resubmission

Regarding your plan to submit, over the subsequent months, portions of a Complete Response to our Complete Review letter of May 18, 2007: as you are aware, “a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.” It will not be possible to submit a complete response until after the Advisory Committee because information from the Advisory Committee may importantly impact the contents of your response to the May CR letter. We encourage you to thoroughly evaluate the discussions from that meeting when developing your response. However, we do invite you to submit your responses to questions 1a-1d of the May 18, 2007 CR letter in advance of the complete response.

With respect to your request for "agreement" regarding the classification of the response to the May 18, 2007 letter, we cannot make a decision on the classification of the resubmission until we have received the submission and the review team agrees that you have addressed all the issues.

Regarding the structure, timelines and your role for the September Advisory Committee, as discussed in the teleconferences, the focus of the meeting is 1) the safety of erythropoiesis-stimulating agents as a class; and 2) available data regarding “Quality of Life” claims. We do not intend to discuss the specific data regarding the safety and efficacy of Mircera. Therefore, if you wish to present your data at the Advisory Committee, you must inform us no later than June 18 so that we can make appropriate changes to the meeting agenda to incorporate a discussion of the specific data on the safety and efficacy of Mircera.

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,



Karen Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

BLA: 125164

Product: PegEpo

Sponsor: Roche

Today's date: June 12, 2007

Speakers: Rick Pazdur for FDA and Cindy Dinella for Roche

FDA: Rick Pazdur, Karen Weiss, Dwaine Rieves, Ruyi He, John Lee and Florence Moore

Roche: Cindy Dinella, Lisa Luther, Philippe Van der Auwera, Bruno Osterwalder, Chris Dougherty Krishnan Viswanadhan

This telephone conference was a follow up to the June 11, 2007 telephone conversation with Roche regarding Roche's perspective concerning any need for Roche to present their data at a September advisory committee that had been planned to focus upon class issues with the ESAs.

FDA stated that regarding Roche's intent to submit, over the subsequent months, portions of a Complete Response to our Complete Review letter of May 18, 2007, a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed. It will not be possible to submit a complete response until after the Advisory Committee because information from the Advisory Committee may importantly impact the contents of Roche's response to the May CR letter. FDA encouraged Roche to thoroughly evaluate the discussions from that meeting when developing their response. Nevertheless, FDA invited Roche to submit their responses to questions 1a-1d of the May 18, 2007 CR letter in advance of the complete response.

FDA reiterated that the purpose of the AC meeting is to discuss the class of ESAs and not for a specific approval. Mircera falls under this class and the labeling for all ESAs will apply to Mircera. FDA stated that a decision on the approvability of Mircera has been made and does not intend to discuss the approvability of Mircera at the AC meeting. However, even though the decision has been determined FDA need to work with the other ESA applicants to come to an agreement that will apply to all the ESA labels, if FDA cannot come to an agreement with all the sponsors for a common label this will hold up the decision to approve Mircera.

Roche expressed concern that their product would be held up because of the FDA/other sponsor's disagreements and requested that an action be taken on Mircera soon after the AC meeting, and assured FDA that they will promptly incorporate any agreeable and applicable changes made to all the ESA labels. FDA stated that if Roche guarantee to

make the applicable changes than it is doable to take a decision on Mircera by its due date. Roche also requested that their resubmission be classified as a type 1 submission once it is submitted after the AC meeting. FDA indicated that we cannot make that decision now but would most likely classify the resubmission a type 1 submission.

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