



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202799

**NDA APPROVAL
REMS APPROVAL**

Affymax, Inc
Attention: Diane Ingolia, Ph.D
Executive Director
4001 Miranda Avenue
Palo Alto, CA 94304

Dear Dr. Ingolia:

Please refer to your New Drug Application (NDA) dated May 27, 2011, received May 28, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OMONTYS[®] (peginesatide) Injection.

We acknowledge receipt of your amendments dated June 8, 23, 2011, July 15, 18, 19, 28, 29, 2011, September 23, 23, 30, 2011, October 3, 5, 26, 2011, November 10, 22, 23, 2011, December 15, 22, 28, 2011, January 13, 20, 25, 27, 2012, February 2, 10, 13, 15, 2012, March 15, 19, 20, 21, 23, and 24, 2012.

This new drug application provides for the use of OMONTYS[®] (peginesatide) Injection for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

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

Based on the provided stability data, an 18-month expiration dating period is granted for the drug product when stored at 2-8 °C, protected from light, and retained in carton until time of use.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, patient instructions of use and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).”

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202799.**” Approval of this submission by FDA is not required before the labeling is used.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages 0 to 12 months because necessary studies are impossible or highly impracticable. This is because there are too few children with anemia associated with chronic kidney disease to study and significant blood volume constraints exist in this age group with this condition.

We are deferring submission of your pediatric studies for ages 1 to 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required trials are listed below.

PMR-1884-1	Phase 2 open-label trial to evaluate the safety, efficacy and pharmacokinetics of peginesatide injection for maintenance treatment of anemia in pediatric subjects with chronic kidney disease (CKD) on hemodialysis who are currently stable on ESA therapy.
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Draft Protocol Submission: 09/2012
Final Protocol Submission: 03/2013
Trial Completion: 05/2016
Final Report Submission: 12/2016

PMR-1884-2 Phase 2 open-label follow-up trial to evaluate the safety, tolerability, and efficacy of peginesatide injection for maintenance treatment of anemia in pediatric subjects with CKD on hemodialysis.

Draft Protocol Submission: 03/2013
Final Protocol Submission: 09/2013
Trial Completion: 10/2016
Final Report Submission: 05/2017

PMR-1884-3 Phase 3 randomized, active-controlled, open-label, multicenter trial to evaluate the efficacy and safety of peginesatide injection for maintenance treatment of anemia in pediatric subjects with CKD on dialysis.

Draft Protocol Submission: 11/2016
Final Protocol Submission: 05/2017
Trial Completion: 06/2025
Final Report Submission: 01/2026

PMR-1884-4 Phase 3 open-label follow-up extension trial to evaluate the safety, tolerability and efficacy of peginesatide injection for maintenance treatment of anemia in pediatric subjects with CKD on dialysis.

Draft Protocol Submission: 06/2017
Final Protocol Submission: 12/2017
Trial Completion: 06/2026
Final Report Submission: 01/2027

Submit the protocols to your IND 63257, with a cross-reference letter to this NDA.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of increased adverse cardiovascular events associated with OMONTYS[®](peginesatide) Injection treatment of patients with CKD.

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

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

- PMR-1884-5: Post marketing comparative observational safety study of dialysis patients (both incident and prevalent) receiving Omontys versus a U.S. marketed ESA to assess safety of long term use. Provide the protocol and analysis plan for FDA review and concurrence prior to commencing the study. The between-group comparison must balance by site and by patient characteristics that are important for cardiovascular, stroke and mortality outcome. Pre-specify the study questions, the testable hypothesis and analysis plan.

The timetable you submitted on March 20, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2012
Final Protocol Submission:	02/2013
Study Completion:	07/2016
Final Report Submission:	03/2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of increased fatal cardiovascular and/or thromboembolic adverse events associated with peginesatide treatment of patients with CKD, specifically incident dialysis patients.

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

- PMR-1884-6: Conduct a prospective randomized, controlled trial (RCT) of Omontys versus a U.S. marketed ESA in anemic patients with chronic kidney disease (CKD) who are in the time interval around the initiation of dialysis (defined as incident dialysis patients for this purpose) and at least a

reasonable proportion (to be decided during the protocol development) who have not received an ESA previously. Continue the trial through the stabilization period on dialysis and the maintenance period on dialysis sufficient to assess the comparative safety (and efficacy) of Omontys using a primary outcome of Major Adverse Cardiovascular Events (MACE) with supporting safety evidence including SAEs, AEs leading to discontinuation, and study/drug discontinuations. Use a blinded independent panel to adjudicate potential MACE events. Stratify randomization for important adverse cardiovascular risk factors. Justify the sample size and risk ratio chosen to evaluate the MACE endpoint. Justify the choice of active control comparator and dosing plan for both treatment arms. Assess transfusion use and identify the reasons that transfusions are given (e.g., active bleeding, pre-op for a procedure, and symptoms).

Submit the full protocol for FDA review and FDA concurrence before beginning enrollment and by end of 09/2012.

The timetable you submitted on March 20, 2012, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2012
Final Protocol Submission:	03/2013
Trial Completion:	08/2018
Final Report Submission:	08/2019

Submit the protocols to your IND 63257, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for OMONTYS[®] (peginesatide) Injection to ensure the benefits of the drug outweigh the serious risks of potentially fatal cardiovascular and/or thromboembolic adverse events, and the increased risk of these events in patients with CKD not on dialysis.

We have determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on March 26, 2012, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS. You are required to submit REMS assessments to the FDA at 12 months, 24 months, 36 months and in the 7th year from the date of initial approval of the REMS.

Your REMS must be fully operational before you introduce OMONTYS[®](peginesatide) Injection into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. The results of surveys of OMONTYS[®] (peginesatide) Injection prescribers establishing:
 - a. the diagnoses of patients for whom the prescriber uses OMONTYS[®] (peginesatide) Injection, including the dialysis status of the patients;
 - b. prescriber knowledge of the risks of potentially fatal cardiovascular and/or thromboembolic adverse events in dialysis patients with receiving OMONTYS[®] (peginesatide) Injection, and the increased risk of these events in non-dialysis patients, should such patients receive OMONTYS[®] (peginesatide) Injection.
2. Use data regarding the prescribing and dispensing of OMONTYS[®] (peginesatide) Injection; that is, how much (and percent) OMONTYS[®] (peginesatide) Injection is used within dialysis centers, how much (and percent) OMONTYS[®] (peginesatide) Injection is used outside of dialysis centers, how much (and percent) is administered to/by patients receiving dialysis, how much (and percent) is administered to/by patients who do not receive dialysis, and the diagnoses for use.

The source of each data point should be described.

3. Data establishing the number and specialty of health care providers (HCPs) targeted via email, the number and specialty of HCPs who received the email, and number and specialty who opened the email, number of emails that were undeliverable, the number of letters sent hard copy and distributed by sales representatives, the names of professional organizations contacted to distribute the DHCP letter to their members, the names of the organizations who accepted and redistributed the letter, and the names of the professional organizations who declined to accept or redistribute the DHCP letter.
4. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 202799 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 202799 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 202799
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 202799
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

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

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

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

POST-ACTION FEEDBACK MEETING

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

If you have any questions, call Ebla Ali Ibrahim, Lead Regulatory Health Project Manager, Acting at (301) 301-796-3691.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

Content of Labeling
Carton and Container Labeling
REMS

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

/s/

RICHARD PAZDUR
03/27/2012