

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202799Orig1s000**

**OFFICE DIRECTOR MEMO**

### Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Richard Pazdur, MD
<b>Subject</b>	Office Director Decisional Memo
<b>NDA/BLA #</b>	202799
<b>Supplement #</b>	
<b>Applicant Name</b>	Affymax, Inc.
<b>Date of Submission</b>	5/27/11
<b>PDUFA Goal Date</b>	3/27/12
<b>Proprietary Name / Established (USAN) Name</b>	Omontys (peginesatide)
<b>Dosage Forms / Strength</b>	Solution for injection: Intravenous (IV) or Subcutaneous (SC) use/supplied in single use and multi-use vials, pre-filled syringes (multiple strengths)
<b>Proposed Indication(s)</b>	is an erythropoiesis-stimulating agent (ESA) that is indicated for the treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis.  is not indicated for the treatment of anemia in CRF patients not on dialysis or for the treatment of anemia due to cancer chemotherapy
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Division Director Summary Review	Ann Farrell, MD
Medical Officer Review	Andrew Dmytrijuk, MD/Kathy Robie-Suh, MD, PhD
Statistical Review	Qing Xu, PhD/Mark Rothmann, PhD
Pharmacology Toxicology Review	Kimberely Ringgold, PhD/Brenda Gehrke, PhD/Haleh Saber, Ph.D./John Leighton, PhD
CMC Review/OBP Review	Li-Shan Hiseh, PhD/Janice Brown, PhD and Sarah Pope-Miksinski, PhD and K. Riviere, PhD/Sandra Suarez Sharp, PhD
Microbiology Review	Denise Miller, PhD
Clinical Pharmacology Review	Young J. Moon, PhD/Julie Bullock, PhD
DDMAC	
OSI	Anthony Orenca, MD
CDTL Reviews	Kathy Robie-Suh, MD, PhD
OSE Reviews	
Labeling Reviews	Latonia Ford, RN/James Dvorsky
Other – Pediatrics Maternal Health Team Division of Cardiorenal Drug Products	Shona Pendse, MD

## 1. Introduction

The applicant has submitted an NDA for peginesatide an intravenously and subcutaneously administered synthetic (not biologic) erythropoiesis stimulating agent (ESA).

The FDA has approved three biologic products drugs for use in the treatment of anemia due to chronic kidney disease/failure. All these biologic products are administered parenterally: Epogen/Procrit (epoetin), Aranesp (darbepoetin), and Micera (never marketed).

The major safety issue that has arisen over the past 15 years with these products is a concern for serious adverse events, including all-cause mortality and arterial thromboses related in some way to the use of ESAs to raise hemoglobin (Hgb) levels in CKD.

From the ODAC briefing document for this application:

*The main sources of this new safety information were controlled clinical trials published between 1998 and 2009, namely the "Normal Hematocrit Study" (NHS study) (Besarab et al. 1998), the "Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) study" (Singh et al. 2006) and the "Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)" (Pfeffer et al. 2009).*

*These studies, designed to show superiority in cardiovascular outcomes by targeting higher Hgb levels with the ESAs, demonstrated that this method of therapy increased the risk of cardiovascular adverse events, including – all cause mortality, MI, and/or stroke in those patients treated with ESAs to achieve higher hemoglobin (Hgb) target levels. Current scientific knowledge remains unclear to what extent the ESA dose, the ESA regimen, the hemoglobin rate of rise, the achieved hemoglobin value, the failure to achieve the target hemoglobin (thus requiring additional ESA dose), or some other factor(s) may account for the observed effects in these trials. The Agency reviewed these trials and subsequently revised the prescribing information (PI) for the use of ESAs for the anemia of CKD...*

This submission contains the results of 4 trials (2 trials in patients with CKD on dialysis and 2 trials in patients with CKD not on dialysis) to support this NDA. AFX01-12 and AFX01-14 are phase 3 randomized, controlled, open label, multicenter studies in patients with CKD on dialysis. AFX01-11 and AFX01-13 are phase 3 randomized, controlled, open-label, multicenter studies in patients with CKD not on dialysis. For all four trials, the primary efficacy analysis was a comparison of the mean change in hemoglobin between the baseline and the evaluation period (weeks 29 to 36 for studies AFX01-12 and 14 and weeks 25-36 for studies AFX01-11 and 13). For all four trials, based on the pre-specified efficacy analysis plan for each trial, the applicant has concluded and FDA agrees that peginesatide is non-inferior to the comparator (epoetin or darbepoetin).

From the ODAC briefing document:

*The major concern raised by these trials is the uncertainty about the evidence for the safety of peginesatide. The trials were sized to assess safety, and the applicant prespecified that the primary analysis of the safety outcomes for each trial should be performed using a safety composite endpoint and that the results should be compared using 90% confidence intervals. The composite safety endpoint (CSE), defined as the first occurrence of any one event of death, stroke, myocardial infarction, congestive heart failure, unstable angina, or arrhythmia, was the primary protocol specified safety endpoint for analysis. An additional planned safety analysis was to be performed assessing the MACE composite endpoint – major adverse cardiac events (defined as the first occurrence of death, stroke or myocardial infarction). The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE and the MACE endpoints. However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for peginesatide. Differences in baseline characteristics unfavorable to peginesatide are acknowledged. Using the applicant's pre-specified primary safety analysis plan and the CSE outcomes, the safety of peginesatide appears to be statistically significantly inferior to darbepoetin. However, using the applicant's secondary analysis plan*

*comparing MACE outcomes, and using a 95% confidence interval, the safety outcomes for peginesatide are numerically worse, but they are not statistically significantly different from that of the darbepoetin-treated group. Statistical testing of the safety outcomes is appropriate since these were prespecified outcomes for analysis and were considerations in determining the sample sizes. Also, the trial results must be considered in the context of safety of the ESA comparator (in this case, darbepoetin), which in and of itself is confounded by safety concerns as were discussed above.*

## 2. CMC/Device

The CMC review team recommends that this application be approved, pending an overall acceptable recommendation from the Office of Compliance. Stability data support an 18-month expiration dating period for the drug product when stored at 2-8 °C, protected from light, and as retained in carton until time of use.

The Office of Compliance 2/17/12 review did not find any issues which would preclude approval.

## 3. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

Based on the available data, peginesatide is being categorized as Pregnancy C category. The toxicological profile of peginesatide was consistent for erythropoietin-stimulating agents with changes in red blood cell hematology parameters (red blood cells, hemoglobin, and hematocrit) and morphology, enlarged spleens, and increased hematopoiesis/hypercellularity and hyperplasia in the bone marrow. Peginesatide was not carcinogenic in the rat and in Tg.rasH2 transgenic mice studies.

## 4. Clinical Pharmacology/Biopharmaceutics

There are no clinical pharmacology issues that preclude approval. The following is from the clinical pharmacology review:

*Peginesatide is not metabolized and it is not an inducer/inhibitor of CYP enzymes. Peginesatide does not bind to serum albumin or lipoproteins. Four phase 1 cross-over studies evaluated the bioequivalence of test formulations of SDV, MDV and PFS to the reference 10 mg/mL SDV formulation. These studies suggested equivalent PK and PD across the proposed range of commercial formulations.*

No significant QTc prolongation effect of AF37702 injection was detected in this TQT study.

## 5. Clinical Microbiology

The Microbiology Team recommends approval.

## 6. Clinical/Statistical-Efficacy

The sponsor submitted the final results from 4 randomized clinical trials and several phase 2 trials exploring initiating treatment with peginesatide in patients on dialysis but not on ESA treatment, long term safety studies (up to 54 months treatment) and interim results in a small trial enrolling patients with anemia due to CKD who developed erythropoietin-mediated pure red cell aplasia.

For all four trials, the primary efficacy analysis was a comparison of the mean change in hemoglobin between the baseline and the evaluation period (weeks 29 to 36 for studies AFX01-12 and 14 and weeks 25-36 for studies AFX01-11 and 13). For all four trials, based on the pre-specified efficacy analysis plan for each trial, the applicant has concluded and FDA agrees that peginesatide is non-inferior to the comparator (epoetin or darbepoetin).

From the statistical review by Dr. Xu:

*The primary efficacy endpoint for all trials was change in hemoglobin between the baseline and the evaluation period. The non-inferiority margin was 1.0 g/dL for all trials. Peginesatide would be considered non-inferior to the comparator if the lower limit of the two-sided 95% CI for the difference between the two treatment groups' mean changes of hemoglobin (Peginesatide - Epoetin) from baseline was  $\geq -1.0$  g/dL for the non-dialysis trials. Each trial met this noninferiority criterion.*

## 7. Safety

The major concerns with this application are the safety concerns seen with the other ESAs (biological products). These concerns are the increased risks of death, myocardial infarction, stroke, thromboses (venous and arterial), tumor progression and immunogenicity (development of pure red cell aplasia).

From the statistical review by Dr. Xu

*The phase 3 clinical program includes an assessment of cardiovascular (CV) safety utilizing blinded adjudication of pre-specified CV endpoints. The Phase 3 dialysis and non-dialysis studies were pooled for the primary CSE analysis, as well as analyzed by population (dialysis and non-dialysis). The CSE was defined to consist of the following six component events: death, stroke, myocardial infarction (MI), congestive heart failure (CHF), angina and arrhythmia. Composite endpoint (defined as the first occurrence of death, stroke or myocardial). The time to first CSE event was analyzed by estimating HRs using stratified Cox regression for each study...*

*The safety outcomes in both on-dialysis trials (AFX01-12 and AFX01-14) appear similar for both treatment groups for both the CSE (HR=0.94, 95% CI= (0.76, 1.16)) and the MACE (HR=0.84, 95% CI= (0.66, 1.09)) endpoints. However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes, with results unfavorable for Peginesatide. The HR was 1.28 with 95% CI of (0.94, 1.75) for CSE endpoint, and the HR was 1.34 with 95% CI of (0.88, 2.05) for MACE endpoint.*

The Agency conducted additional sensitivity analyses and other exploratory analyses which did not provide evidence that an imbalance in baseline disease, demographic factors or other factors impacted the overall suggestion of a higher risk for the patients with anemia due to CKD who are not receiving dialysis.

Other important adverse events observed include hypertension, gastrointestinal disturbances (nausea, vomiting, diarrhea), and dyspnea.

From Dr. Robie-Suh's CDTL memo she makes the following recommendations:

*Because peginesatide is dosed once monthly instead of biweekly to three times a week as for currently marketed ESA agents, I think there is a strong potential for off-label use of the drug in patients who are not on dialysis simply due to convenience. Therefore, a risk management plan such as the sponsor has proposed to educate prescribers to the use and risks of the drug and restriction of the distribution of the drug to dialysis centers is appropriate.*

*The labeling of the drug should carry the Boxed Warning and other class labeling as for the other ESAs.*

*Exact wording of the labeling should be negotiated with the sponsor.*

*Post-marketing studies should be required as follows:*

- The sponsor should conduct an adequate and well-controlled study in dialysis patients not yet stabilized on an ESA. The study should be randomized, double-blind (double-dummy, if necessary), active controlled with a primary cardiovascular safety endpoint. The protocol for the proposed study should be submitted for FDA review.*
- To satisfy PREA requirement the sponsor should conduct studies of peginesatide in pediatric patients age 1 year and older with chronic kidney disease on dialysis. Full protocols should be submitted for review prior to study initiation. A waiver should be granted for patients less than 1 year of age.*
- Because treatment with peginesatide is likely to be life-long upon initiation of treatment, the sponsor should plan and conduct a study to gain long-term safety information about use of the drug.*
- The sponsor should complete and submit the ongoing study AFX01-06 of peginesatide therapy that is being conducted in patients with anemia associated with CKD who have a history of antierythropoietin antibodies.*

## 8. Advisory Committee Meeting

This product was discussed at an Oncologic Drugs Advisory Committee meeting on December 7, 2011. The Committee voted 15 (yes), 1 (no), and 1 (abstain) that the available clinical data demonstrate a favorable risk-benefit profile for peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis.

## 9. Pediatrics

From the clinical team leader draft memo:

*No pediatric information is included in this submission. The sponsor plans pediatric studies in patients age 1 year and older and seeks a waiver for patients <1 year of age.*

A waiver was granted for studies in patients less than 1 year of age. A deferral has been granted for studies in patients aged 1 year or older.

Pediatric trial requests are included in the approval letter. The study requests are phase 2 and phase 3 trials on the use of ESAs in pediatric patients with anemia due to CKD receiving dialysis or hemodialysis.

## 10. Other Relevant Regulatory Issues

From Dr. Anthony Orenca's Office of Scientific Investigation Summary Review:

*Two U.S. and two foreign clinical investigator sites, plus Sponsor (Affymax, Inc.), were inspected in support of this application. Based on review of inspectional findings for four clinical investigators, the study data collected appear generally reliable in support of the requested indication.*

There are no other unresolved relevant regulatory issues.

## 11. Labeling

The labeling was reviewed by all disciplines and consultant staff and most recommendations were included.

Due to the concern about off-label use in view of the identified safety concerns with other ESAs and the fact that peginesatide has not been extensively studied, several limitations of use were placed in the labeling to discourage the off-label use. In addition the Applicant plans to limit distribution to dialysis centers. These limitations of use include a recommendation not to use this product to treat cancer of anemia and not to use this product to treat patients with anemia due to CKD who are not receiving dialysis.

The labeling will carry class labeling for the ESAs including the Boxed Warning and Warning and Precautions for the increased risk of death, myocardial infarction, venous thromboembolism, thrombosis of vascular access, and tumor progression.

## 12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action  
Regular approval for the use in patients with anemia due to CKD who are receiving dialysis treatment.
- Risk Benefit Assessment  
The risk benefit assessment suggests that peginesatide is effective for the treatment of patients with anemia due to CKD who are receiving dialysis. The risk benefit of the use of peginesatide is not known for the treatment of patients with anemia due to CKD who are not receiving dialysis treatment and therefore this will be a limitation of use. Safety risks are similar to those for the other marketed ESAs

including thrombosis (including death) and hypertension. The safety and effectiveness of peginesatide in the treatment of anemia due to cancer chemotherapy is not known; therefore, there will be a limitation of use to communicate a recommendation not to use. The risk –benefit profile was also discussed in the reviews by Drs. Farrell, Robie-Suh and Dmytrijuk, and I concur with their assessment as well as the review team’s recommendation for approval.

- Recommendation for Post marketing Risk Management Activities  
A REMS is planned to achieve the following goals:

To inform healthcare professionals that Omontys Injection is indicated only for use in the treat of patients with anemia of chronic renal failure on dialysis.

To inform healthcare professionals of the serious risk associated with the use of Omontys Injection including potentially fatal cardiovascular and/or thromboembolic adverse events, and the increased risk of these events in non-dialysis patients.

- Recommendation for other Post marketing Study Requirements/Commitments  
See Action Letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAMY E KIM  
03/27/2012

RICHARD PAZDUR  
03/27/2012