## Summary Review for Regulatory Action

<table>
<thead>
<tr>
<th>Date</th>
<th>(electronic stamp)</th>
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<tbody>
<tr>
<td>From</td>
<td>Ann. T. Farrell, M.D., Acting Division Director</td>
</tr>
<tr>
<td>Subject</td>
<td>Division Director Summary Review</td>
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<tr>
<td>NDA/BLA #</td>
<td>202799</td>
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<td>Supplement #</td>
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<tr>
<td>Applicant Name</td>
<td>Affymax, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>5/27/11</td>
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<td>PDUFA Goal Date</td>
<td>3/27/12</td>
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<tr>
<td>Proprietary Name /</td>
<td>Peginesatide</td>
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<tr>
<td>Established (USAN) Name</td>
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<tr>
<td><strong>Dosage Forms / Strength</strong></td>
<td>Solution for injection: Intravenous (IV) or Subcutaneous (SC) use/supplied in single use and multi-use vials, pre-filled syringes (multiple strengths)</td>
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<tr>
<td><strong>Proposed Indication(s)</strong></td>
<td>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</td>
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<tr>
<td><strong>Action/Recommended Action for NME:</strong></td>
<td>Approval</td>
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### Material Reviewed/Consulted

<table>
<thead>
<tr>
<th>OND Action Package, including:</th>
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</thead>
<tbody>
<tr>
<td>Medical Officer Review</td>
<td>Andrew Dmytrijuk, M.D./Kathy Robie-Suh, M.D. Ph.D.</td>
</tr>
<tr>
<td>Statistical Review</td>
<td>Qing Xu, Ph.D./Mark Rothmann, Ph.D.</td>
</tr>
<tr>
<td>Pharmacology Toxicology Review</td>
<td>Kimberely Ringgold, Ph.D./Brenda Gelirke, Ph.D./Haleh Saber, Ph.D./John Leighton, Ph.D.</td>
</tr>
<tr>
<td>CMC Review/OBP Review</td>
<td>Li-Shan Hiseh, Ph.D./Janice Brown, Ph.D. and Sarah Pope-Miksinski, Ph.D. and K. Riviere, Ph.D./Sandra Suarez Sharp, Ph.D.</td>
</tr>
<tr>
<td>Microbiology Review</td>
<td>Denise Miller, PhD.</td>
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<tr>
<td>Clinical Pharmacology Review</td>
<td>Young J. Moon, Ph.D./Julie Bullock, Ph.D.</td>
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<td>DDMAC</td>
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<td>OSI</td>
<td>Anthony Oencia, M.D.</td>
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<tr>
<td>CDTL Reviews</td>
<td>Kathy Robie-Suh, M.D. Ph.D.</td>
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<tr>
<td>OSE Reviews</td>
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<tr>
<td>Labeling Reviews</td>
<td>Latonia Ford, R.N./James Dvorsky</td>
</tr>
</tbody>
</table>

**Other – Pediatrics**

- Maternal Health Team
- Division of Cardiorenal Drug Products

| Products | Shona Pendse, M.D. |

Reference ID: 3106215
1. Introduction

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

The following text is the Applicant’s proposed indication:

*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*

2. Background

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, Aranesp, 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 for all four trials 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.

3. CMC/Device

Drs. Hsieh and Pope-Miksinski reviewed this supplement. In their review they state the following:

This New Drug Application for Omontys® (Peginesalide) Injection, Single use vials (preservative-free):
2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL.
Single use pre-filled syringes (preservative-free):
1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL.

Multiple use vials (with preservative):
10 mg/mL and 20 mg/2 mL

is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending an overall acceptable recommendation from the Office of Compliance and receipt of acceptable final labeling.

Also note that there is a pending issue regarding the which was discussed with the Applicant on 25-JAN-2012. As a result of that teleconference, the Applicant agreed to provide additional justification for the proposed acceptance criterion.

The Applicant provided additional pharmacological justification for the proposed acceptance criterion, and the adequacy of this information is currently under review by the Pharmacology/Toxicology reviewer. This is not an approvability issue from a CMC perspective, and any administrative changes (ie decreases to the specification for will be captured in a subsequent CMC memo as needed.

The following language needs to be inserted into the action letter:
Based on the provided stability data, an 18-month expiration dating period is granted for the drug product when stored at 2-8 ºC, protected from light, and as retained in carton until time of use.

From the statistical analysis of the stability profile:

This review describes statistical findings on Affymax Inc’s data from stability study under long term storage condition (2 – 8 ºC) so that FDA office of New Drug Quality Assessment can make informed decisions on the proposed shelf life of the drug product.

Due to large number of strengths, batches, and storage conditions, the sponsor employed a reduced stability design, matrixing design. Based on statistical analysis on 12-month stability data, the sponsor concluded that the shelf life of the drug product can be safely extrapolated up to , the proposed shelf life. The FDA statistician conducted independent statistical analysis on the sponsor’s stability data. The shortest among 70 estimated shelf lives is 37 months. Since the drug product is intended to be stored in a refrigerator, the maximum extrapolation that can be considered is 6 months beyond the period covered by long-term data. The sponsor’s long-term data is either month long. Therefore, the statistical analysis supports the extrapolation of a shelf life to the proposed for 2 mg, 3 mg, and 4 mg PFS drug products, 2 mg SDV drug product, and 20 mg MDV drug product. However, a shelf life can be extrapolated to only 18 months for 1 mg and 6 mg PFS drug products, 4 mg and 6 mg SDV drug products, and 10 mg MDV drug product. The shelf life for 3 mg SDV drug product cannot be established because one of three primary batches was rejected and excluded from the analysis.

The Office of Compliance review did not find any issues which would preclude approval. Their review dated 2/17/12 found the submission acceptable.

Reference ID: 3106215
4. Nonclinical Pharmacology/Toxicology

Drs. Gehrke and Ringgold wrote in their review:

The nonclinical studies submitted to this NDA provide sufficient information to support the use of peginesatide for the treatment of anemia due to chronic kidney disease in adult patients on dialysis.

Based on the available data Peginesatide is a Pregnancy C category based on nonclinical data. 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.

From Dr. Saber’s review:

OMONTYS® (peginesatide) is an erythropoiesis-stimulating agent (ESA). Peginesatide is a synthetic, pegylated dimeric peptide. The two identical peptide chains are covalently attached through a linker derived from iminodiacetic and β-alanine. The amino acid sequence of peginesatide is not related to that of erythropoietin (EPO), however, peginesatide binds to and activates the recombinant human erythropoietin receptor with high specificity. Peginesatide showed activities similar to EPO and approved ESAs, Aranesp and Epogen/Procrit. Therefore, the pharmacologic class assigned to peginesatide is “erythropoiesis-stimulating agent”, to be consistent with the label for Aranesp and Epogen/Procrit. The pharmacologic class is described in INDICATIONS AND USAGE in the HIGHLIGHTS section of the label. Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in in vitro systems and/or in animal species. Peginesatide was administered subcutaneously or intravenously to animals in toxicology studies, consistent with the intended route of administration in patients. Drug-related toxicities were similar after subcutaneous or intravenous administration and after single- or repeat-dose administration. Only repeat-dose general toxicology studies were reviewed for this NDA. Toxicities were mostly related to pharmacology of the drug and were consistent with those observed with marketed ESAs.

Adverse effects in animals included: increased RBCs, hemoglobin, and hematocrit, enlarged spleens, and increased hematopoiesis/hypercellularity and hyperplasia in the bone marrow. Increased congestion was seen in multiple organs. Cardiac toxicity (thrombosis, stromal proliferation of the atrio-ventricular valve, and myocardial degeneration) was evident in rats after ≥3 months of dosing. There were no adverse cardiac conduction findings, based on the results of the hERG study and the ECG parameters assessed in the monkey in the toxicology study. Hemoco-concentration was speculated to be the cause of cardiac toxicity and multi-organ congestion. Renal toxicities were mostly evident in the rat and included tubular degeneration, dilated tubules with cytoplasmic vacuolation, and congestion/inflammation.
Peginesatide was not genotoxic in the ICH battery of genotoxicity assays or carcinogenic in the rat and in Tg.rasH2 transgenic mice.

5. Clinical Pharmacology/Biopharmaceutics

From the clinical pharmacology review by Dr. Moon:

Peginesatide is not metabolized and it is not an inducer/inhibitor of CYP enzymes. Peginesatide does not bind to serum albumin or lipoproteins. Clinical development of peginesatide has primarily utilized a single-dose vial (SDV) formulation at a drug concentration of 10 mg/mL. Peginesatide concentrations from 2 to 12 mg/mL are planned for marketing as SDV, in addition to a multiple-dose vial (MDV) and a pre-filled syringe (PFS). 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.

There are no issues which would preclude approval of peginesatide based on the clinical pharmacology reviews.

From the IRT review:
No significant QTc prolongation effect of AF37702 injection was detected in this TQT study.

From the Office of Biopharmaceutics within the Office of New Drugs Assessment; This application is recommended for approval from a Biopharmaceutics standpoint. A waiver for the CFR BA/BE requirement is granted for the following strengths of the proposed products:
• SDV: 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL
• PFS: 1 mg /0.5 mL, 2 mg /0.5 mL, 3 mg /0.5 mL, 4 mg /0.5 mL, and 6 mg/0.5 mL

6. Clinical Microbiology

The Microbiology Team recommended approval in their review.

7. 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 chronic kidney disease who developed erythropoietin-mediated pure red cell aplasia.

For all four trials, the primary efficacy analysis for all four trials 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 applicant submitted data and final study reports of four phase 3 randomized, controlled, open label, multicenter trials to seek full approval for Peginesatide injection for the indication of “Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis”. In the NDA, there are two trials (AFX01-11 and AFX01-13) in patients with CKD on dialysis and two trials (AFX01-12 and AFX01-14) in patients with CKD not on dialysis.

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.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for both indications.

8. 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 applicant submitted data and final study reports of four phase 3 randomized, controlled, open label, multicenter trials to seek full approval for Peginesatide injection for the indication of “Treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis”. In the NDA, there are two trials (AFX01-11 and AFX01-13) in patients with CKD on dialysis and two trials (AFX01-12 and AFX01-14) in patients with CKD not on dialysis…

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.

I concur with the conclusions of the clinical and statistical review teams regarding the analyses of safety.

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 antierthropoietin antibodies.

I agree with Dr. Robie-Suh’s recommendations regarding post-marketing requirements and most of these will be incorporated into the action letter.

9. Advisory Committee Meeting
This product was discussed at a 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.

10. 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.

11. Other Relevant Regulatory Issues
Office of Surveillance and Epidemiology was consulted as well as other divisions involved in labeling.

From Dr. Anthony Oencia’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.
12. **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.

A REMS is planned. From Dr. Kane’s review:

*The goals of the REMS are:*

- To inform healthcare professionals that OMONTYS Injection is indicated only for use in the treatment of patients with anemia due to chronic kidney disease on dialysis.
- To inform healthcare professionals of the serious risks associated with the use of OMONTYS Injection including potentially fatal cardiovascular and/or thromboembolic adverse events, and the increased risk of these events in nondialysis patients.

*The elements of the REMS to achieve these goals will be a communication plan with DHCP letter and a timetable for submission of assessments of the REMS. The communication plan will include a DHCP letter, website, and information on the cardiovascular risks, the lack of evidence of safety or efficacy in other patient populations, and dosing information to achieve appropriate hemoglobin levels based on current labeling for all ESAs.*

13. **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.

- **Recommendation for Post marketing Risk Management Activities**
  REMS program

  Education program for practitioners and limited distribution program

- **Recommendation for other Post marketing Study Requirements/Commitments**
  Conduct a comparative observational safety study of dialysis patients (both incident and prevalent) receiving Omontys versus alternate ESAs to assess safety of long term use.
  Conduct a prospective randomized, controlled trial (RCT) of Peginesatide versus a U.S. marketed ESA drug 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 some of whom 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 Peginesatide using a primary outcome of MACE events.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
03/23/2012