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APPLICATION NUMBER:

202799Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 6, 2012
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	202799
Applicant	Affymax, Inc.
Date of Submission	May 23, 2011, received May 27, 2011
PDUFA Goal Date	March 27, 2012
Proprietary Name / Established (USAN) names	OMONTYS®/ peginesatide
Dosage forms / Strength	Injection (single use vials [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 prefilled syringes [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 [10 mg/mL and 20 mg/2 mL])
Proposed Indication(s)	for the treatment of anemia associated with chronic renal failure (CRF) in adult patients on dialysis
Recommended:	Approval for the indication: OMONTYS® is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis who have been stabilized on an erythropoiesis-stimulating agent.

1. Introduction

In patients with chronic kidney disease (CKD) the prevalence of anemia is strongly associated with worsening renal failure, due largely to deficiency of endogenous erythropoietin. Consequently, patients with CRF on dialysis are anemic and require exogenous erythropoiesis stimulation to maintain a hematocrit sufficient to avoid requirement for red blood cell (RBC) transfusion. Erythropoiesis stimulating agents (ESAs), including Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa) and Mircera (pegylated epoetin alfa) are approved for reducing need for RBC transfusions in patients with CRF on dialysis and not on dialysis. Currently only Epogen/Procrit and Aranesp are marketed. All three of these ESAs are recombinant proteins administered three times a week (Epogen/Procrit), once weekly or once every two weeks (Aranesp), or once every two weeks or monthly [maintenance] (Mircera). In the current application the sponsor (applicant) proposes introduction of peginesatide as another ESA for use in adult patients with CRF on dialysis. Peginesatide (AF37702) is a synthetic, pegylated dimeric peptide that binds to and activates the human erythropoietin receptor (HuEPOr) stimulating erythropoiesis similar to other ESAs. The intended starting dose is 0.04 to 0.08 mg/kg as a single monthly dose for patients not currently receiving an ESA or is to be based on the total weekly dose of current ESA for patients being converted from another ESA. Peginesatide is to be administered intravenously (IV) or subcutaneously (SC) and the maximum human dose, regardless of route of administration, is 0.35 mg/kg.

Regulatory meetings for peginesatide that were held prior to NDA submission included a Type B CMC meeting on February 1, 2007, an End-of-Phase 2 (EOP2) meeting on February 23, 2007 and a Pre-NDA meeting on October 21, 2010.

Peginesatide is not approved in any country and has not been marketed anywhere in the world.

2. CMC/Device

Peginesatide (AF37702) is a synthetic, pegylated dimeric peptide comprised of two identical, 21-amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β -alanine. The molecule has a molecular weight of about (b) (4) Da. It is water-soluble with an unbuffered pH of 7.1 to 8.5. Structurally, the amino acid sequence of peginesatide is not related to that of endogenous erythropoietin. The product (OMONTYS[®] [peginesatide] Injection) is a solution available in multiple strengths as preservative-free single use vials and syringes and as multiple use vials containing phenol (b) (4).

The chemistry, manufacturing and controls (CMC) information in the application has been reviewed by L-S Hsieh, Ph.D., Office of New Drug Quality Assessment (ONDQA) (review signed 1/31/2012). The review found no outstanding deficiencies in the application. The review stated that Omontys "...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". The review recommended

that the action letter include the statement: “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 as retained in carton until time of use.”

The CMC review mentions a pending issue regarding the (b) (4) proposed acceptance criterion. This issue was resolved and an overall acceptable recommendation given by the Office of Compliance (S Pope Mikinski, Ph.D., 3/6/2012). Approval of the application is recommended from a CMC perspective.

The Biopharmaceutics Review (K Riviere, Ph.D., ONDQA, signed 1/18/2012) comments that while the composition of the commercial formulation for the single-dose vial and the pre-filled syringe is the same as was used in the Phase 3 studies, the proposed formulation of the multiple-dose vial is a higher strength than was studied in the clinical trials. Accordingly, a bioequivalence study was conducted to support the approval of the 12 mg/mL strength; and a bioequivalence study of the 10 mg/mL and 2 mg/mL single-dose vial formulations was also conducted. Audit of the analytical portion of the studies found the data from the studies acceptable for review (YM Choi, Division of Bioequivalence and GLP Compliance, 12/22/2011). These studies were reviewed in the Clinical Pharmacology Review (Y-J Moon, Ph.D., final signature 2/8/2012), and found to support bioequivalence. The Biopharmaceutics review states that, “based on 21 CFR 320.22 (b)(1), a waiver for the BA/BE requirements may be granted for all the lower strengths given that the proposed product is a solution and the composition of the commercial formulation is similar to that tested in the Phase 3 trials.” The review recommends approval from a Biopharmaceutic standpoint. And states that a waiver for 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

Methods Validation Report Summary found the data methods acceptable for quality control and regulatory purposes (J Allgire, Division of Pharmaceutical Analysis, 1/30/2012)

Regarding shelf life, the FDA review (Y Jeon, Ph.D., 1/18/12) concluded: “The statistical analysis supports the extrapolation of a shelf life to the proposed (b) (4) 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.” As noted above, the CMC Review (L-S Hsieh, Ph.D., 1/31/2012) indicates that an 18 month expiry, stored at 2-8°C, protection from light is granted.

There were no CMC recommendations for Phase 4 commitments or risk management measures.

3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology review was conducted by K Ringgold, Ph.D. and B Gehrke, Ph.D. (signed 2/2/2012). The review found the submitted nonclinical studies were sufficient to support the use of peginesatide for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. The Pharmacology/Toxicology Supervisor Memorandum by H Saber, Ph.D. (2/27/2012) concurred that “from a nonclinical perspective, OMONTYS may be approved for the proposed indication” without additional nonclinical studies. There were no recommendations for post-marketing studies.

As stated in the Pharmacology/Toxicology Supervisor Memorandum (H Saber, Ph.D., 2/27/2012), 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. The Memorandum indicated that peginesatide showed activities similar to EPO and approved ESAs, Aranesp and Epogen/Procrit and that therefore, the pharmacologic class assigned to peginesatide is “erythropoiesis-stimulating agent”, to be consistent with the label for Aranesp and Epogen/Procrit.

The Pharmacology/Toxicology Supervisor Memorandum summarizes the pharmacology, safety pharmacology, pharmacokinetic/ADME and toxicology findings of the review as follows:

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. Hemo-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.

When administered intravenously during the period of organogenesis, peginesatide was teratogenic to rats and rabbits or caused embryo-fetal lethality.

Peginesatide may reduce male and female fertility. Administration of the drug to male and female rats in a dedicated fertility study, resulted in reduced weight of seminal vesicles and prostate, and decreased viable fetuses in females. The effects in females may be the result of pre- and post-implantation losses. There was no apparent drug-related effect on estrous cycles or number of corpora lutea. Increased morphological abnormalities of the sperm was reported in the pharmacology/toxicology review. Upon further examination of the data, there are no drug-related morphological abnormalities in the sperm. Reduced sperm count was also observed in males and reported in the pharmacology/toxicology review; however, the Applicant provided data indicating that values are within the historical range.

Regarding the Pregnancy Category the applicant proposed a Category C and provided justification for the proposal. The Pharmacology/Toxicology Supervisor Memorandum indicates that the Division of Hematology Oncology Toxicology finds the Category C acceptable and consistent with the labels for the marketed ESAs, Aranesp and Epogen/Procrit. Review.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was conducted by YJ Moon, Ph.D. (final signature 2/8/2012). Because the cardiovascular safety outcomes were similar between treatment arms in the dialysis studies [which required enrolled patients to be on stable ESA doses prior to study] but were dissimilar between treatment arms with results unfavorable for peginesatide in the non-dialysis studies, exploratory analyses were done to seek better understanding of the relationship between poor initial hemoglobin response, ESA dose and cardiovascular outcomes. The review states:

An exploratory analysis was conducted for the non-dialysis population to evaluate the association between poor initial hemoglobin response, subsequent dose and CV outcomes. This analysis identified a subgroup of "slow" responders who had a poor initial response to peginesatide, required higher overall doses to reach the hemoglobin target, and had greater risk for CV events. However, it is not possible with the existing data to conclude that the increased CV risk in this subgroup is due to the higher doses. This subgroup of patients also had an increase in baseline CV risk factors compared to patients who had a better initial hemoglobin response. Similar findings for darbepoetin were reported for the TREAT study and are reflected in the ARANESP product label (sections 2.2, 5.1).

The CV risk in all dialysis patients has not been characterized in the application. The high-risk subgroup of "slow/poor" responders was not studied in the dialysis clinical trials. The on-dialysis trials only enrolled patients who, at baseline, were already on a stable epoetin doses and had hemoglobin within the target of 10–12 mg/dL. These patients were switched from epoetin to peginesatide to maintain hemoglobin within the target. However, the sponsor is seeking an indication for all dialysis patients, including initiation of treatment as well as converting from another ESA product.

Also, based on results of a phase 2 study where 0.04 mg/kg and 0.08 mg/kg starting doses of peginesatide were studied for initiating treatment in ESA-naïve patients on dialysis and results showed similar mean time course and mean hemoglobin with the two dosages, the review recommended that the lower peginesatide dose be used. The review states:

The lower starting dose of 0.04 mg/kg is recommended for initiating treatment in dialysis patients. Based on a phase 2 study, the sponsor has proposed a starting dose range of 0.04 mg/kg to 0.08 mg/kg. In this study, the mean time course and mean hemoglobin for the 0.04 mg/kg and 0.08 mg/kg starting doses were similar. Furthermore, the average dose during the evaluation period was 0.05 for both dose groups. Because the 0.04 mg/kg had an adequate hemoglobin response and CV safety was not evaluated in this phase 2 study, starting doses greater than 0.04 mg/kg are not justified.

The review commented that peginesatide is not metabolized and is not an inducer/inhibitor of CYP enzymes.

The review indicates that cross-over bioequivalence studies of the single-dose vial, multiple-dose vial, and pre-filled syringe formulations suggest equivalent PK and pharmacodynamics across the proposed range of commercial formulations.

The review made the following recommendations:

- We recommend limiting the indication to those dialysis patients studied in the phase 3 clinical trials. The CV safety for dialysis patients initiating peginesatide treatment has not been evaluated.
- If the FDA Office of New Drugs approves peginesatide for all dialysis patients, we recommend a starting dose of 0.04 mg/kg instead of the proposed dose range (0.04 mg/kg to 0.08 mg/kg) for patients initiating treatment.

Labeling recommendations were provided in the review.

There were no recommendations for post-marketing studies.

5. Clinical Microbiology

Omontys is a product for intravenous (IV) or subcutaneous (SC) injection.

The Product Quality Microbiology Review of the application was conducted by DA Miller (signed 2/1/2012). The single-dose vials and multi-dose vials are to be manufactured by Takeda Pharmaceutical Company in Japan and the pre-filled syringe is to be manufactured by (b) (4). Sterilization is to be accomplished by (b) (4). The review finds the application acceptable and recommends to approve from a quality microbiology standpoint. The review has the following comment for the applicant:

“At the Takada manufacturing site, the bioburden sample is taken after the (b) (4). This sample point does not assess the quality control on the formulation of the bulk drug product. A bioburden sample point prior to the (b) (4) should be considered.”

6. Clinical/Statistical- Efficacy

The sponsor conducted four randomized, active-control, open-label trials in patients with chronic kidney disease, two in patients on dialysis (AFX01-12 and AFX01-14) and two in patients not-on dialysis (AFX01-11 and AFX01-13). With regard to efficacy the Clinical Review (A Dmytrijuk, final signature 2/7/2012) concluded:

- The efficacy of the proposed therapy is supported by two trials (AFX01-12 and AFX01-14) conducted in adult patients with anemia associated with CKD who were on dialysis and in two trials (AFX01-11 and AFX01-13) conducted in adult patients with anemia associated with CKD who were not on dialysis. These were similarly designed, randomized, active control, multi-center, open label studies. The goal of the studies was to maintain Hgb levels in the protocol's target range of 10-12 g/dL. Peginesatide, compared to ESA, can be considered non-inferior in terms of efficacy for both groups of patients, i.e., those who were on dialysis and those who were not on dialysis based on the protocol specified efficacy analysis. The lower limit two-sided 95% or 97.5% confidence interval (CI) difference between the two treatment group's mean changes of hemoglobin (Hgb) from baseline was > -1.0 g/dL as shown below:
 - Dialysis Least Squares Mean and 95% CI
 - AFX01-12
 - Peginesatide 0.04 mg/kg starting dose = -0.15 (-0.30,-0.01)
 - AFX01-14
 - Peginesatide 0.04 mg/kg starting dose = 0.10 (-0.05, 0.26)
 - Not-on Dialysis Least Squares Mean and 97.5% CI
 - AFX01-11
 - Peginesatide 0.025 mg/kg starting dose = 0.03 (-0.19,0.26)
 - Peginesatide 0.04 mg/kg starting dose = 0.26 (0.04, 0.48)
 - AFX01-13
 - Peginesatide 0.025 mg/kg starting dose = 0.14 (-0.09,0.36)
 - Peginesatide 0.04 mg/kg starting dose = 0.31 (0.08, 0.54)

The Statistical Review (Q Xu, 2/7/2012) states:

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 ≥ -1.0 g/dL for the non-dialysis trials. Each trial met this non-inferiority criterion.

7. Safety

The major clinical safety concerns relate to increased cardiovascular risk that has been seen in large trials of ESAs in patients with chronic kidney disease (particularly the Normal Hematocrit, CHOIR, CREATE and TREAT studies) which have led to recent major revisions of the safety information in the product labeling for the approved ESAs. [See Clinical Reviews by A Dmytrijuk, M.D. (final signature, 2/7/2012), K Robie Suh, M.D., Ph.D. (dated 2/29/2012, signed 3/9/2012), and Statistical Team Leader Review Memo by M Rothmann, Ph.D. (signed 2/7/2012)].

The Clinical Review (A Dmytrijuk, M.D., final signature 2/7/2012) states:

The major safety concern raised by these trials is the uncertainty regarding cardiovascular safety of peginesatide use in patients with anemia associated with CKD who are not on dialysis. The trials were sized to assess safety, and the applicant pre-specified that the primary analysis of the safety outcomes for each disease setting should be performed using a safety composite endpoint. The outcomes were compared using 90% confidence intervals. The composite safety endpoint (CSE), defined as the first occurrence of death, stroke, MI, CHF, unstable angina, or arrhythmia, was the primary protocol specified safety endpoint for the analysis. An additional planned safety analysis was to be performed assessing the MACE (major adverse cardiac events) composite endpoint, 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. Patients in these studies had hemoglobin levels which were previously stabilized with ESA.

However, in the two non-dialysis trials (AFX01-11 and AFX01-13), there are differences in the safety outcomes for the two treatments, with results unfavorable for peginesatide. 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, the secondary analysis comparing MACE outcomes and using a 95% confidence interval, shows that although the safety outcomes for peginesatide are numerically worse, the outcomes are not statistically significantly different from that of the darbepoetin-treated group.

The benefit risk ratio favors the approval of peginesatide for the treatment of patients with anemia associated with CKD who are on dialysis in whom previous erythropoiesis-stimulating agent (ESA) therapy has been stable.

The Statistical Review for the application (Q Xu, Ph.D., 2/7/2012) concludes:

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 Statistical Team Leader Review Memo (M Rothmann, 2/7/2012) provides additional comments on the limitations of the studies conducted, particularly for the safety analyses and recommends:

Should peganesatide get approved for CKD patients on dialysis, my recommendation is that the indication correspond with the inclusion/exclusion criteria of the AFX-012 and AFX-014 studies, which includes subjects having stable dosing on epoetin for a minimum of eight weeks. Additionally, studies with CKD patients on dialysis should be conducted to assess the safety (and efficacy) of peganesatide corresponding to the usage specified in the label. Studies should also be conducted evaluating initial use for the treatment of anemia in patients with CKD on dialysis. For safety evaluation purposes, I recommend that the studies be stratified by age and New York Heart Association failure class.

A consult was obtained from the Division of Cardiovascular and Renal Products (DCRP) requesting the Division to “evaluate and advise on the significance of the finding of adverse safety for Peginesatide in the not-on-dialysis population versus the on-dialysis.” The consult review by SS Pendse, M.D. (final signature 11/16/2011) indicated that there was no obvious biologically plausible mechanism for a differential risk for adverse cardiovascular outcomes for the non-dialysis versus the dialysis population. The review also noted that the 95% confidence intervals [for the adverse cardiovascular endpoints] overlap, suggesting that there may be no difference between the two populations with regard to cardiovascular risk with peginesatide relative to marketed ESA products. The review also cited concerns regarding factors that might have contributed to bias in the studies, such as the lack of blinding and relatively high rates of study discontinuation. The review commented:

Perhaps the most critical issue is that these trials characterized the risk of Peginesatide relative to marketed ESAs. Why, unless the other agent offers significant advantage over marketed ESAs, would one tolerate 1.3 times greater risk of adverse CV outcomes above and beyond that of marketed ESAs? The fact that we do not know the safety profiles of the chosen comparators makes it extremely difficult to evaluate the safety of Peginesatide against the backdrop of these active comparators. It is concerning, nonetheless, that the available data do not allow for the exclusion of excess risk with Peginesatide therapy relative to existing ESA comparators, in a population with a high absolute risk of CV disease at baseline.

The DCRP review provided recommendations for trial designs for future studies to evaluate comparative safety among ESA products. The review did not make recommendations for approvability of the application.

8. Advisory Committee Meeting

A meeting of the Oncologic Drugs Advisory Committee was held on December 7, 2011 to discuss the NDA for peginesatide for the indication for the treatment of anemia associated with chronic kidney disease in adult patients on dialysis. Results for the studies in patients on dialysis and in patients not on dialysis were presented. The major concern from these trials is the uncertainty about the safety of peginesatide, as reflected in an apparently worse outcome

for cardiovascular safety in patients not on dialysis who received peginesatide as compared to other ESA. Following the discussion, the following question was put to the Committee:

“Is there a favorable benefit to risk evaluation for peginesatide for use in patients with anemia associated with chronic renal failure who are on dialysis?”

The Committee voted: 15 Yes; 1 NO; 1 Abstain.

Comments voiced during the presentation of the vote included concern for the non-blinded design of the trials, concern that the dialysis population studied may have been too narrow to detect a safety signal and concern for potential mis-use of peginesatide in the non-dialysis population.

9. Pediatrics

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.

The clinical review (A Dmytrijuk, final signature 2/7/2012) comments:

Globally, the prevalence of chronic kidney disease (CKD) stage II or lower in children is reported to be approximately 18.5-58.3 per million children. Disease prevalence is much lower than that in adults. The author states that a mean incidence of 12.1 cases per year per million in the age-related population (age range, 8.8-13.9 years) and a prevalence of 74.7 per million in this population. The author also states that the frequency of chronic kidney disease increases with age. Among children, chronic kidney disease is more common in children older than 6 years than in those younger than 6 years.¹⁰ A waiver for the study of peginesatide in pediatric patients < 12 months of age due to low prevalence of anemia secondary to CKD in this age group who are on dialysis and not undergoing kidney transplantation should be given. A deferral for studies in pediatric patients (age ≥ 12 months to < 18 years) with CRF on dialysis should also be given.

10. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspected two U.S. and two foreign clinical investigator sites and the Sponsor. The Clinical Inspection Summary (A Orenca, M.D., Division of Good Clinical Practice Compliance, OSI, signed 12/16/2011) states, “Based on the review of inspectional findings for four clinical investigators, the study data collected appear generally reliable in support of the requested indication.” The review indicated that for the foreign clinical sites observations are based on preliminary communications for the field investigator.

The Clinical Review (A Dmytrijuk, final signature 2/7/2012) notes that two investigators who had enrolled patients into one or more of the four major clinical studies had received payments in excess of \$25,000. The sponsor stated that the potential for bias due to these payments was minimal because one investigator enrolled only (b) (4) of a total 493 subjects in Study AFX01-13

and (b) (4) of 823 subjects in Study AFX01-14 and the other investigator enrolled (b) (4) of 823 subjects in Study AFX01-12. The Clinical Review found the explanation acceptable.

The Division of Medication Error Prevention and Analysis (DMEPA) (YL Maslov, 12/23/2011) evaluated the labeling for vulnerabilities that may lead to medication errors for Onontys. The review identified a potential issue of syringe leakage and needle separation with the type of pre-filled syringe (i.e., (b) (4) DMF (b) (4) Type III) to be used with Onontys and recommended that, “since other packaging configurations for this product are available such as single dose and multi-dose vials, we do not recommend the approval of pre-filled syringe that uses (b) (4) syringe until the Applicant conducts thorough extensive mechanical testing and human factors studies.” The review also provided recommendations for the product labeling (package insert and cartons and packaging).

The final Proprietary Name Review (YL Maslov, Pharm.D., final signature 2/22/2012) found no objection to the proprietary name, Omontys, for this product at this time.

11. Labeling

The sponsor included proposed labeling in the submission. Exact wording for the labeling is being developed by the review team incorporating the recommendations from each of the review disciplines and consulting review divisions.

12. Recommendations/Risk Benefit Assessment

The sponsor has provided adequate demonstration of efficacy and an acceptable benefit/risk profile for peginesatide for use in dialysis patients as studied in their major clinical trials. Because there is only limited data on safety and efficacy of peginesatide in patients with chronic kidney disease on dialysis who have not been stabilized on other ESAs prior to exposure to peginesatide and because of the known but not fully understood cardiovascular risk associated with these agents, strong consideration should be given to restricting use of Omontys (peginesatide) to dialysis patients known to tolerate and respond to available ESAs. Additional studies are needed to clarify the safety and efficacy of peginesatide in ESA-naïve patients on dialysis.

- Omontys (peginesatide) injection is acceptable for approval for the indication:

OMONTYS® is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis who have been stabilized on an erythropoiesis-stimulating agent.

- The dosing in individual patients should be based on current ESA dose as was done in the clinical trials.
- The product label should carry the same Boxed Warning and other class labeling as the currently approved ESA products.
- The exact wording of the labeling should be negotiated with the sponsor.
- Risk management for peginesatide should focus on ensuring that only the labeled population is prescribed the drug (such as via a restricted distribution program and physician education).
- 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 anti-erythropoietin antibodies.
- Strong consideration should be given to requiring the following post-marketing studies:
 - 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.
 - 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.
 - To satisfy PREA requirement the sponsor should be required to 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 pediatric studies in patients less than 1 year of age.

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/s/

KATHY M ROBIE SUH
03/10/2012