

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202799Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: March 26, 2012

Reviewer(s): Joyce Weaver, Pharm.D., Risk Management Analyst
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Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., RMA Team Leader, DRISK

Division Director: Claudia Karwoski, Pharm.D., Director, DRISK

Drug Name(s): Peginesatide (Omontys)

Therapeutic Class: Erythropoiesis-stimulating agent (ESA)

Dosage and Route: Initially, 0.04 mg/kg body weight once monthly by intravenous or subcutaneous injection; for patients converting from other ESA therapy, 2-20 mg injection monthly

Application Type/Number: NDA 202799

Applicant/sponsor: Affymax, Inc

OSE RCM #: 2011-2555

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EXECUTIVE SUMMARY

The applicant has submitted a REMS comprising a communication plan and a timetable for submission of assessments incorporating all changes negotiated between the applicant and the FDA. The REMS is needed to mitigate the risks of potentially fatal cardiovascular and thromboembolic adverse events, and the increased risk of these events in non-dialysis patients. DRISK recommends approval of the REMS submitted March 23, 2012.

1 INTRODUCTION

1.1 BACKGROUND

Peginesatide (Omontys) is a synthetic erythropoiesis-stimulating agent (ESA) structurally unrelated to the currently marketed recombinant ESAs. Peginesatide is receiving consideration at the Agency for initial approval for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

1.2 REGULATORY HISTORY

The application for Omontys was filed May 27, 2011 and was discussed at a meeting of the Oncologic Drugs Advisory Committee (ODAC) on December 7, 2011. ODAC agreed that the drug showed efficacy and safety for the proposed indication (CKD on dialysis) and found the risk-benefit profile to be favorable.

2 MATERIALS REVIEWED

We reviewed the proposed REMS, REMS materials, and REMS Supporting Document submitted March 22, 2012 and March 23, 2012, submitted in response to Agency comments, dated March 12, 2012, and discussed in a meeting between the applicant and the Agency conducted by telephone March 19, 2012 .

3 RESULTS OF REVIEW OF PROPOSED OMONTYS RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

Peginesatide was studied in four clinical trials conducted in adult CKD patients with anemia, two trials in patients who were on dialysis, and two trials in patients who were not on dialysis. The trials were randomized, active control, multi-center, open-label studies. Target hemoglobin (Hgb) levels in the trials was 10-12 g/dL. Peginesatide was non-inferior to the comparator ESA for both patients on dialysis and patients not on dialysis based on the pre-specified endpoints.

3.2 SAFETY CONCERNS

Safety was a primary outcome objective in the trials and was evaluated by comparing adverse events, serious adverse events, deaths, adverse events grade 3 or greater, and adverse events leading to permanent discontinuation. In addition, two composite safety endpoints were specified by the applicant, one involving six cardiovascular (CV) events and another consisting of major objective adverse cardiovascular (MACE) events. In the

patients randomized in the two on-dialysis trials, the safety events were very similar between the two arms, and the MACE outcome, numerically but not statistically, favored the peginesatide arm over the epoetin arm. However, in the non-dialysis trials, the percentage of safety events observed was greater in peginesatide-treated patients as compared to the darbepoetin control group. A pre-planned analysis of the six item composite safety endpoint chosen by the applicant (including death, stroke, myocardial infarction, congestive heart failure, unstable angina, and arrhythmia) showed a greater occurrence of these events in peginesatide-treated non-dialysis patients compared to the control group (hazard ratio [HR] 1.32, 90% confidence interval [CI] = 1.02, 1.72).

When the safety analysis was narrowed to the MACE events of death, stroke, and myocardial infarction, there were more MACE events in the non-dialysis patients receiving peginesatide compared to the non-dialysis patients receiving darbepoetin, but the difference was not statistically significant using the analytic tests usually accepted by CDER (HR 1.41, 95% CI = 0.92, 2.16).

Because peginesatide has not been tested in patients with cancer, it is not known if peginesatide confers increased risk of tumor progression in oncology patients.

3.3 PROPOSED REMS

The applicant voluntarily submitted a REMS proposal with the application to address the risks of cardiovascular events with ESAs and the increased risk of cardiovascular events in non-dialysis patients. The proposed REMS included a Medication Guide, a communication plan, and a timetable for submission of assessments to address the . Subsequently, the FDA and the applicant agreed that the Omontys Medication Guide would not be an element of the REMS.

The REMS ultimately determined by the Agency to be necessary to assure that the benefits of peginesatide outweigh its risks is outlined below.

3.3.1 Goals

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 of 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 non-dialysis patients.

3.3.2 REMS ELEMENTS

3.3.2.1 Medication Guide

The Omontys Medication Guide is not an element of the REMS.

3.3.2.2 Communication Plan

A Dear Healthcare Professional (DHCP) letter will be sent within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 12 months. The letter will be available via a REMS-specific link from the Omontys website and through the medical information department for 2 years following approval of the REMS. The intended audience for this letter is the nephrology community of Healthcare Professionals (HCPs) who are likely to prescribe Omontys.

3.3.2.3 Elements to Assure Safe Use

The Omontys REMS does not include elements to assure safe use.

3.3.2.4 Implementation System

The Omontys REMS does not include an implementation system.

3.3.2.5 Timetable for Submission of Assessments

The sponsor will submit REMS Assessments at 12, 24, 36 months and in the 7th year from the date of initial approval of the REMS.

3.4 REMS ASSESSMENT PLAN

The REMS Assessment Reports will include 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 establishing the site of 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.

4 DISCUSSION

Following the favorable recommendation regarding the Omontys application at the December 7, 2011 ODAC meeting, an internal regulatory briefing was held January 13, 2012 to discuss the safety concerns for patients with CKD not on dialysis. Although the regulatory briefing is not a decisional meeting, the discussion was generally positive for approval with the indication limited to CKD on dialysis as proposed.

Risk mitigation for Omontys was presented to the REMS Oversight Committee (ROC) on February 3, 2012, and in a meeting between the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) on February 8, 2012¹. The issue discussed at the February 8 meeting was whether a REMS is needed as part of the approval for Omontys (peginesatide) NDA for the purpose of ensuring that potential risks are considered for off-label uses where safety is uncertain and are consistent with approved ESAs.

Discussion focused on the risk mitigation needed for peginesatide given that the other ESAs have a REMS comprising a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments.

The meeting participants considered the following:

- Is a REMS needed to limit possible off-label use by CKD patients not on dialysis?

¹ Participants included Ebla Ali Ibrahim, Gerald Dal Pan (by phone), Andrew Dmytrijuk, Ann T Farrell, John K Jenkins, Robert Kane, Sue Kang, Claudia B. Karwoski, Mwango Kashoki, Tamy Kim, Cynthia LaCivita, Diane V. Leaman, Richard Pazdur, Joyce Weaver

- Is a REMS needed to limit possible off-label use in patients with cancer (considering the ESA REMS)?
- Can Omontys be approved for the labeled indication (CKD on dialysis) without a REMS but with PMRs to monitor for off-label uses (in oncology and CKD not on dialysis) and with strong limitation of use statements in the indication section for both of the off-label concerns?

The possibility was discussed that this product could be used for oncology patients with anemia, to avoid the REMS requirements associated with use of the other ESAs in oncology patients. The ESA REMS focuses on safe use in oncology patients. The goals of the ESA REMS are: 1) to support informed decisions between patients and their healthcare providers (HCPs) who are considering treatment with Aranesp by educating them on the risks of Aranesp and, 2) for treatment of patients with cancer: the goal of the REMS as implemented through the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs {erythropoiesis stimulating agents}) Oncology Program, is to mitigate the risk of shortened overall survival and/or increased risk of tumor progression or recurrence.

After discussion, the meeting participants decided that the REMS for peginesatide would focus on off-label use in CKD patients not receiving dialysis for a number of reasons: 1) the risk of tumor progression has not been established with peginesatide, 2) it will not receive approval for use in oncology patients, and 3) its off-label use in oncology is largely unknown. For these reasons, the team determined that an oncology-focused class REMS, required for the other ESAs, is not appropriate for peginesatide.

Consensus was reached at the February 8 meeting for the following:

- 1) Strengthen the labeling for limitations of use and safety.
- 2) A REMS comprising a communication plan directed to the nephrology prescribing community and then to all new peginesatide prescribers not previously included in the communication. The communication plan should be comprised of a Dear Health Professional letter describing the safety risk regarding use in non-dialysis patients with anemia; that is, the increase in MACE events observed in the clinical trial, and safety information regarding appropriate target hemoglobin. The Medication Guide for Omontys will not be part of the REMS.
- 3) Drug use data to be reported within the REMS assessment reports to assess use in the non-dialysis patient population and in oncology practice.

The decision to require a communication plan was to inform prescribers of the cardiovascular risks, especially the increased risk in CKD patients not on dialysis, and to communicate dosing information to achieve appropriate hemoglobin levels based on current labeling for all ESAs.

5 CONCLUSION

In conclusion, the amended REMS for Omontys (peginesatide) injection, March 23, 2012 contains the appropriate and agreed upon revisions on the REMS components. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the Omontys REMS in achieving the goals.

Therefore, the Omontys REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the Omontys REMS submitted March 23, 2012.

Language for the approval letter regarding information needed for REMS assessments was provided previously.

ATTACHMENTS

Initial REMS approval 03/2012

NDA 202799

OMONTYS[®] (peginesatide) Injection
An erythropoiesis-stimulating agent (ESA)

Affymax, Inc.
4001 Miranda Avenue
Palo Alto, CA 94304
Phone: 855-466-6689

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To inform healthcare professionals that OMONTYS Injection is indicated only for use in the treatment of patients with anemia of 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 non-dialysis patients.

II. REMS ELEMENTS

A. Communication Plan

Affymax, Inc. will implement the following elements of a communication plan:

1. A Dear Healthcare Professional (DHCP) letter will be sent within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 12 months. The letter will be available via a REMS-specific link from the OMONTYS website and through the medical information department for 2 years following approval of the REMS. The intended audience for this letter is the nephrology community of Healthcare Professionals (HCPs) who are likely to prescribe OMONTYS.

The letter will be sent to all nephrologists, to related professional societies, and to dialysis facilities. Dialysis facilities and professional societies receiving the DHCP letter will be requested to distribute the DHCP letter to their staff, including other HCPs, or membership.

In addition, for 18 months following approval of the REMS, new nephrologists and new dialysis facilities ordering OMONTYS will receive the letter if they have not previously received it. The list of HCPs to receive the letter will be derived from a comprehensive commercially available database.

Within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 12 months, Affymax, Inc. will send the DHCP letter to the following professional organizations, and will request that the letter be provided to the members of the professional organizations:

National Renal Administrators Association (NRAA)
American Society of Nephrology (ASN)
Renal Physicians Association (RPA)
American Nephrology Nurses Association (ANNA)
National Kidney Foundation (NKF)

The letter will be provided to MedWatch at the same time it is provided to the professional organizations.

The letter will be available at the OMONTYS booth at the following scientific meetings for the two years following approval of OMONTYS:

American Nephrology Nurses Association (ANNA)
National Kidney Foundation (NKF)
National Renal Administrators Association (NRAA)
American Society of Nephrology (ASN)
Renal Physicians Association (RPA)

The Dear Healthcare Professional letter is part of the REMS and is appended.

The communication plan will be updated to reflect any changes in labeling for the risks outlined above.

Affymax, Inc. will make the REMS, the DHCP letter, and professional labeling available via a REMS-specific link from the OMONTYS website as well as through the medical information department for 2 years after the initial date of approval.

The OMONTYS REMS web page is part of the REMS; the landing page screen shot is appended.

B. Timetable for Submission of Assessments

Affymax, Inc. will submit REMS Assessments to FDA at 12, 24, 36 months and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that

assessment. Affymax, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1: Dear Healthcare Professional Letter

IMPORTANT DRUG WARNING

Subject: Increased risk of cardiovascular events in patients with Chronic Kidney Disease (CKD) not on dialysis

Dear Healthcare Professional:

Affymax, Inc. and Takeda Pharmaceuticals America, Inc. would like to inform you that OMONTYS[®] (peginesatide) Injection, an erythropoiesis-stimulating agent (ESA) for once monthly administration, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis only.

In collaboration with the FDA, a Risk Evaluation and Mitigation Strategy (REMS) has been developed to ensure the benefits of Omontys outweigh the risks.

Omontys is not indicated in patients with CKD not on dialysis

- In two trials of Omontys, patients with CKD not on dialysis experienced increased specific cardiovascular events.

We remind you that all ESAs, including Omontys have a **boxed warning** containing the following:

ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence

- In controlled clinical trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks
- Use the lowest Omontys dose sufficient to reduce the need for red blood cell transfusions

Medication Guide

A Medication Guide is provided to medical personnel and nephrology societies to facilitate the education of dialysis patients on the risks of Omontys.

[Guidance for Medical Personnel- include in Dear HCP letter]:

- At the start of Omontys therapy, when needed to reinforce patient knowledge, and when new information is included in the Medication Guide, provide and review the current Medication Guide with each patient and/or patient caregiver

IMPORTANT DRUG WARNING

[Guidance for Nephrology societies include in professional society letter]

- Raise awareness among the membership for the need of the medical personnel to provide a Medication Guide as outlined above

Copies of the Omontys Medication Guide, may be obtained from the website www.omontys.com or by calling Affymax at 1-855-466-6689.

Reporting Adverse Events

To report all adverse events suspected with the use of Omontys contact:

- Affymax at 1-855-466-6689.
- FDA's MedWatch reporting system by phone (1-800-FDA-1088), or online (www.accessdata.fda.gov/scripts/medwatch)

This letter is not a comprehensive description of the risks associated with the use of Omontys. Please read the accompanying Full Prescribing Information and Medication Guide for a complete description of these risks.

Affymax and Takeda are committed to working in partnership with you to support medical personnel and patient education regarding the safe use of Omontys in patients with anemia of CKD on dialysis.

Sincerely,

Appendix 2: REMS-specific Link on OMONTYS Website – Landing Screen Shot



OMONTYS® (peginesatide) Injection Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

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

OMONTYS is not indicated in patients with CKD not on dialysis.

- In two trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events

OMONTYS has a **boxed warning** containing the following language:

ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

Use the links below to access important REMS documents:

- [Dear Healthcare Professional Letter](#)
- [Prescribing Information](#)
- [Medication Guide](#)

Limitations of Use

OMONTYS is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for RBC transfusions in patients who require immediate correction of anemia. OMONTYS has not been shown to improve symptoms, physical functioning, or health-related quality of life.

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/s/

JOYCE P WEAVER
03/26/2012

CLAUDIA B MANZO
03/26/2012
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Oncology Drug Products
Division of Hematology Products

NDA:	202799
Products:	OMONTYS® (peginesatide) Injection
APPLICANT:	Affymax, Inc
FROM:	Robert Kane, MD; Deputy Director for Safety (acting), DHP
DATE:	March 14, 2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for OMONTYS® (peginesatide) Injection, to ensure that the benefits of the drug outweigh the risks of major adverse cardiovascular events including death. In reaching this determination we considered the following:

- A. Approximately 400,000 patients are receiving dialysis annually in the U.S. The United States Renal Data System (USRDS) is a national data system that collects, analyzes and distributes information about ESRD in the U.S. ESRD is defined by the need for renal replacement therapy (dialysis or transplantation).
- B. The patients for this product, receiving dialysis, have well-recognized increased risks of major adverse cardiovascular events and death, due both to the disease condition and in some circumstances to ESA therapy. Challenges in the care of ESRD patients include managing their underlying co-morbidities, the dialysis procedure and the sequelae from frequent

hospitalizations due to infections, cardiovascular (CV) disease, and vascular access complications. Underlying co-morbidities in the ESRD population include congestive heart failure, atherosclerotic heart disease, cerebrovascular disease, peripheral vascular disease, hypertension, type II diabetes mellitus and other disease states affecting CV function. CV disease is a major cause of morbidity and mortality in the dialysis population and accounts for almost 45% of all deaths in the dialysis patient population. During the 2008 period, death occurred in 88,620 ESRD patients

- C. The expected benefit of the drug to patients is that once monthly dosing offers advantages to the other currently approved erythropoietin-stimulating agents (ESAs), and this synthetic drug offers those who may have hypersensitivity to the biologic ESAs an alternative choice. ESAs, including Omontys, reduce the need for blood transfusions in CKD patients.
- D. The expected duration of treatment with the drug will be for the entire duration of dialysis, which averages three to five years.
- E. The most serious of the known adverse events that are related to the use of all ESAs, including OMONTYS® (peginesatide) Injection, are death, myocardial infarction, stroke, vascular thromboses, and hypertension.
- F. OMONTYS® (peginesatide) Injection is a new molecular entity.

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 non-dialysis 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.

In the initial NDA submission (May 27, 2011), the applicant included a REMS proposal under the assumption that the currently marketed ESAs had REMS plans involving the use of ESAs in CKD. During the final weeks of the FDA review of the NDA, the following considerations led to the decision to require a REMS as now designed. The ODAC committee (December 7, 2011) expressed concern about the safety findings in the not-on-dialysis (NOD) population. A CDER regulatory briefing discussion (January 13, 2012), noting the numeric difference in more safety outcomes for the Omontys study arm of the NOD trials, considered that restricted distribution could be a means to assure safe use, and the company's voluntary plan to achieve that goal could not be considered as binding on the company. A subsequent ROC meeting (February 3, 2012) explored options for assuring safe use, and deferred to a subsequent meeting between OSE and OND to determine.

At the OSE-OND meeting (Feb 8, 2012), a REMS was judged appropriate for the following reasons:

1. There is a numerical difference but not a statistical difference in the MACE outcomes in the trials of CKD NOD, indicating more AEs in the Omontys study arm in trials designed to assess safety endpoints. The overall NDA trial enrollments and study durations were modest (average 1.1 years), and any suggestion of an adverse event signal had to raise additional concern, could potentially involve both patients on dialysis and NOD, and could not be minimized. In each trial, an active comparator was used in the control arm, so the difference had to be judged as possibly being added on top of a baseline safety condition of concern and continuing study (ESA safety).
2. When marketed, Omontys should be used in a different dosing schedule than that used in the clinical trials. The reason is to minimize risk of MACE events, similar to the currently marketed ESAs, by recommending a dose-schedule to achieve similar hemoglobin goals to those currently marketed.
3. There is no evidence of the safety or efficacy of Omontys for use in patients with cancer and anemia related to chemotherapy. While Omontys is not being considered for this indication, this off-label use would be undesirable in the absence of evidence from a trial.
4. Via the REMS, surveys of practitioner knowledge and use of Omontys can be obtained.
5. Proposed drug labeling will present the current safety concerns for all ESAs and incorporate the revised dosing advice (June 24, 2011), but the "uptake" of this information by clinicians remains uncertain. Enhanced communications from sponsor to clinicians can help improve communication of essential safety and dosing concerns.
6. DHP considered additional labeling prerogatives such as contraindications or limitations of use. Limitations of use are appropriate and may help to guide usage to the studied and approved condition. Contraindications are not appropriate since there may be individual patients who might benefit from this drug despite falling outside of the indication as stated.

7. A Medication Guide will be developed. It will be implemented outside of the REMS, as part of labeling.
8. There are concerns with introducing this new REMS. Introducing a REMS for Omontys will likely cause confusion among stakeholders, since the goals and elements of this REMS would differ from the REMS for Epogen and Aranesp and the provider population is the converse of that for the biologic ESAs. This will require monitoring by FDA to ascertain the extent of confusion resulting. However, the Omontys REMS will not directly be requiring special certification or enrollment by patients or prescribers, as does the existing ESA REMS.
9. Note also that DHP is recommending PMRs to further study Omontys safety, as described elsewhere.
10. No imbalance was observed for the risk of cancer development in the clinical trials, either in those with an antecedent history of cancer or as a new event. Thus there is not a safety signal requiring monitoring or mitigation of this concern within the Omontys REMS.

Risk of cancer development in the peginesatide trials:

	Pooled AFX01-12 and AFX01-14 (Dialysis)*		Pooled AFX01-11 and AFX01-13 (Non-Dialysis)**	
	Peginesatide (n=1066), N (%)	Epoetin (n=542) N (%)	Peginesatide (n=656) N (%)	Darbepoetin (n=327) N (%)
Hx of Baseline Malignancy	131 (12)	61 (11)	102 (16)	40 (12)
Malignancy Adverse Event	42 (4)	23 (4)	31 (5)	14 (4)

Addendum:

REMS for the Other marketed ESAs

Both of the marketed recombinant ESAs, Aranesp (darbepoetin alfa) and Epogen/Procrit (epoetin alfa), have REMS. The goals of the REMS for these ESAs are:

1. To support informed decisions between patients and their healthcare providers who are considering treatment with ESA by educating them on the risks of ESA.
2. For treatment of patients with cancer, the goal of the REMS, as implemented through the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs {erythropoiesis stimulating agents}) Oncology Program, is to mitigate the risk of shortened overall survival and/or increased risk of tumor progression or recurrence.

The existing ESA REMS comprises a Medication Guide, a communication plan, elements to assure safe use (certification of prescribers who prescribe for patients with cancer in private practice settings and in hospitals, certification of hospitals, dispense to patients with documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments.

Nephrologists and other HCPs who prescribe for CKD are sent communication by the ESA communication plan only to inform them that the REMS is to mitigate the oncology risks associated with the ESAs. The communication plan does not relay safety information related to the CKD use of ESAs.

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/s/

ROBERT C KANE
03/22/2012