CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

FINAL REMS MODIFICATION REVIEW

Date: June 9, 2011

To: Patricia Keegan, MD, Director
Division of Biologic Oncology Products

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management

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Subject: Erythropoiesis Stimulating Agents (ESAs)
Proposed REMS Modifications Review (2)

Drug Name (Established Name):
Aranesp (darbepoetin alfa)
Epogen (epoetin alfa)
Procrit (epoetin alfa)

Application Type/Number: BLA 103951/5258
BLA 103234/5266
BLA 103951/5173
BLA 103234/5166

Applicant: **Amgen**

OSE RCM #: 2010-550

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Table of Content

1 Introduction

The purpose of this review is to summarize the modifications to the Erythropoiesis Stimulating Agents (ESAs) REMS Document, REMS Supporting Document, and REMS website as agreed upon by the FDA and the Sponsor on June 1, 2011 and submitted by Amgen on June 8, 2011.

2 Background

Amgen proposed a REMS modification on October 14, 2010 which included proposed modifications to the forms and the ESA APPRISE Oncology Program Website. On a November 19, 2010 teleconference, FDA requested Amgen submit an amendment to PAS (submitted 10/14/10) to include modifications to address stakeholder concerns to reduce the burden to the healthcare system in implementing the REMS but that will still be capable of meeting the intent of the REMS. On March 3, 2011, FDA requested that all REMS materials be submitted to the PLR Conversion supplement and cross referenced to the REMS Modification supplement. The sponsor submitted the REMS modifications to the PLR supplement on March 22, 2011.

The following timeline describes the sequence of interactions between the Agency and the Sponsor after the March 22, 2011 submission regarding the proposed REMS modifications.

- **May 06, 2011** – the FDA sent the Applicant a request for information regarding their March 22, 2011 submission (Epoetin alfa (Epogen®/PROCRIT®), Sequence No. 0351 Resubmission of the Physician Labeling Rule (PLR) Prior Approval Supplement (PAS) in Response to Complete Response Letter; Proposed REMS Modifications).
- **May 19, 2011** – the Sponsor responded to the Agency's request for information from May 06, 2011 (EPOGEN®lPROCRIT® (Epoetin alfa) Sequence No. 0364 Epoetin alfa Drug Product Fill Volume IPC Update Amendment: Response to Request for Additional Information)
- **May 31, 2011** – the FDA sent the Sponsor comments on the May 19, 2011 submission and a revised version of the REMS Document.
- **June 1, 2011** – the Sponsor submitted the revised version of the REMS Document
- **June 8, 2011** – the Sponsor submitted the final version of the modified REMS documents via email

The purpose of this review is to evaluate the applicant's responses to the additional information requested by the Agency on May 06, 2011, summarize the modifications to the REMS Document and other REMS materials as agreed upon by the Sponsor and FDA on June 1, 2011, and review the June 8, 2011 submission to verify all changes expected changes have been implemented.

3 Materials Reviewed

DRISK reviewed the following documents:

- Submissions from May 19, June 1, and June 8, 2011 addressing the modifications to the REMS.

4 ESA REMS OVERVIEW

The Erythropoiesis Stimulating Agents (ESAs) have a class REMS to address the risk of shortened overall survival and/or increased risk of tumor progression or recurrence. The REMS consists of a Medication Guide, communication plan, and elements to assure safe use (ETASU). The Medication Guide is directed to any patient treated with an ESA. The communication plan and ETASU apply to the cancer indication. The ETASU includes required prescriber certification, hospital certification, and documentation of safe use conditions through a signed patient-prescriber acknowledgement form.

5 ESAs REMS Modifications Agreed Upon by FDA and the Sponsor

The following sections summarizes the modifications to the ESA REMS as agreed upon by FDA and the Sponsor.

5.1 Modifications to the REMS-Related Documents

5.1.1 Modifications Regarding the Medication Guide

Distribution of the Medication Guide. On May 17, 2011 the Office of Regulatory Policy (ORP), Office of Compliance, DBOP, and DRISK agreed to remove specific details

regarding the Medication Guide distribution in light of the new draft guidance.[1] This resulted in the following modifications to the REMS Document:

a. **REMS Document**

- Deletion of [redacted] (b) (4) with the objective of being consistent with 21 CFR Part 208. All patients receiving treatment with an ESA, regardless of the indication, must receive a Medication Guide in accordance with 21 CFR Part 208 and draft Guidance. However, Oncology patients will receive a Medication Guide as stipulated by the ESA REMS. ORP added to sections C.1.b.4 and C.2.b.4 of the REMS Document the underlined language below to clarify that Healthcare Providers (HCPs) do not have to schedule a monthly appointment with the sole purpose of providing the Medication Guide,

[redacted] (b) (4)

—or, if regular office visits occur less frequently than once a month, at the next regularly scheduled office visit."

- Added the following text to sections C.1 and C.2, "Ensure that printed copies of the Epogen/Procrit Medication Guides are available upon request through the ESA APPRISE Oncology Program Call Center".

b. **Enforcement Discretion Letters.** In addition, on June 2, 2011 the FDA issued Enforcement Discretion Letters indicating the following,

- **Non-cancer patients.** When ESAs are administered by a healthcare provider (e.g., in a physician's office, clinic, hospital inpatient setting, or dialysis center) to patients who do not have cancer, the FDA intends to exercise enforcement discretion with

[1] Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS) DRAFT GUIDANCE. February 20, 2011. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf. Accessed June 9, 2011.

respect to the requirements of 21 CFR 208.24(e) as long as the Medication Guide is provided to each patient or patient caregiver at the initiation of therapy and again if the Medication Guide is materially revised or updated.

- **Oncology patients.** When ESAs are administered by a healthcare provider (e.g., in a physician's office, clinic, hospital inpatient setting, or dialysis center) to patients with cancer, we intend to exercise enforcement discretion with respect to the requirements of 21 CFR 208.24(e) as long as the Medication Guide is provided to each patient or patient caregiver at the initiation of therapy; once a month during regular office visits — or, if regular office visits occur less frequently than once a month, at the next regularly scheduled office visit — for as long as treatment continues; and again if the Medication Guide is materially revised or updated.

5.1.2 Other Modifications

Other noteworthy modifications to the REMS-related materials are described below:

a. Global change (all REMS-related documents): Change of [redacted (b) (4)] to 'shortened overall survival and/or increased risk of tumor progression or recurrence'. This change is consistent with labeling.

b. Global change: Addition of the word 'myelosuppressive' to the oncology indication statement anywhere this is found within the REMS materials.

c. Global change: Deleted the terms [redacted (b) (4)] in the REMS document.

d. REMS Document: Revised the REMS to accommodate for electronic upload, use, and archiving of Acknowledgement Forms. Revisions were made to the Implementation System outlining the "allowable changes" to the Acknowledgement Forms, verbiage was added to the Acknowledgement Forms to reference "allowable changes" and a flashcard was added to the REMS describing the "allowable changes" to healthcare providers.

e. REMS Document: Revised document header to include the standard "initial REMS approval date; date last modified ".

f. REMS Document: Removed [redacted] (b) (4) to make the document concise and consistent with the latest FDA policy and included high-level statements to capture the basic REMS requirements. Certain details were deleted that were already included in the enrollment and Acknowledgement Forms with the objective of making the document more concise and avoiding a future need to modify the REMS Document if additional changes are made to the enrollment forms.

g. REMS Document: Deleted [redacted] (b) (4)

h. REMS Document: Changed [redacted] (b) (4) ' to "patient representative".

i. REMS Document: Changed [redacted] (b) (4) ' to "agree".

j. REMS Document and Website: FDA did not agree with the proposed text on page 14 under, Implementation System D.1.a of the REMS Document, [redacted] (b) (4); [redacted] and requested Amgen also modify similar language in the 'Guidelines for Patient Acknowledgement Form Integration within Healthcare Systems and Clinics' flashcard.

k. REMS Supporting Document: FDA recommended modifying the REMS Supporting document, page 12, section 3.3.1.5, (Healthcare Delivery System Impact and Patient Access, item #2 Requirement for all HCPs and Hospitals to use the ESA APPRISE Oncology Program Patient Acknowledgement Form without modification as a paper-based form), by deleting the first two paragraphs and summarizing the actions already taken to address the problems encountered with the Acknowledgement Form.

l. Website: Modification to the Q&A section of the website: Modified the reply to the question, "What are the consequences of not training and enrolling in the ESA APPRISE Oncology Program?" to reflect the fact that the enrollment grace period has already concluded. The new reply reads, "Failure to comply with program requirements, including training and enrollment [redacted] (b) (4) will result in suspension of access to ESAs".

m. Website: Deletion of redundant text in the webpages.

n. Website: Revised the homepage to increase the visibility of the risk.

5.2 Sponsor Responses to FDA Comments

5.2.1 Response to FDA Comment 1

Changes to the internet homepage. The Sponsor agreed to the changes suggested by FDA but included the following modifications which the FDA accepted:

- Reinserted the names of the companies in the first sentence of the second paragraph.
- Modified the 2 main bullets under the sub-heading "What are the risks addressed by the ESA APPRISE Oncology program?"describing the risks with the objective of maintaining alignment with the USPI in PLR format.
- Added the following sentence under the Key Program Requirements table for clarification purposes 'Note that patient registration or approval through the ESA APPRISE Oncology program is not required.'
- Added the term 'myelosuppressive' to the indication statement to align with the USPI.
- Modified the following bullet under 'ESAs are not indicated for use in:' to align with the USPI.
    - 'in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure;'

FDA considered that listing Key Program Requirement in a table format was a good suggestion by the Sponsor but recommended the proposed table to be restructured for space efficiency. The Sponsor concurred.

5.2.2 Response to FDA Comment 2

"Allowable Changes" to Patient Acknowledgement Form. The Sponsor agreed to:

- Modify Section 3 of the ESA APPRISE Oncology Program Training Module for Healthcare Providers and the ESA APPRISE Oncology Program Training Module for

Hospital Designees in order to highlight the availability of the "Guidelines for Patient Acknowledgement Form Integration within Healthcare Systems and Clinics" flashcard.

- Add a hyperlink to the flashcard within the training modules contained on the website.
- Edit the hard copy Training Module to include directions that the guidelines flashcard is accessible at www.esa-apprise.com in the Forms and Resources section.

FDA concurred with these changes.

5.2.3 Response to FDA Comment 3

HCP Enrollment Form. The Sponsor agreed with FDA's recommendations to modify the HCP enrollment form to add a second sub-bullet to be consistent with the current draft USPI and requested FDA to retain the language for the third bullet to avoid language that could be interpreted as dictating the practice of medicine. A global change from (b) (4) to 'agree' was done throughout the REMS materials.

The FDA concurred with these changes.

5.2.4 Response to FDA Comment 4

HCP and Hospital Designee Training Modules: The Sponsor agreed with FDA recommendations to align the language in the HCP Training Module with that in the USPI. Similar changes were also implemented in the Hospital Designee Training Module.

5.2.5 Response to FDA Comment 5

Re-printing of REMS Materials. The Sponsor confirmed that the REMS materials will be re-printed as soon as possible after finalization of the REMS modification supplement and will take into consideration the upcoming name change for Centocor Ortho Biotech Products.

FDA concurred.

5.2.6 Response to FDA Comment 6

Correction of Several Errors. The Sponsor concurred with FDA proposed corrections except for corrections described in 6a for which they propose the following language:

Original text: "Your enrollment identification number will be required on every patient acknowledgement form".

Revised text by Sponsor: [redacted] (b) (4)

FDA concurred.

5.2.7 Response to FDA Comment 7

Modification of Dear Healthcare Provider Letters (DHCPL). The Sponsor requested clarification of FDA point described in 7a. FDA withdrew this comment and agreed the Sponsors will modify the original Dear Healthcare Provider Letters (DHCPL) and include these as part of the continuing Communication Plan. This change is reflected in the revised version of the REMS Document. DRISK and the Division of Drug Marketing, Advertising and Communications (DDMAC) reviewed the revised versions of DHCPL sent by the Sponsor June 3, 2011and provided comments on June 6. The Sponsor sent on June 8, 2011 revised versions of the DHCPLs including FDA proposed changes.

The FDA concurs with the Sponsor implementation of FDA proposed modifications in comment 7b.

6 Conclusion and Recommendations

DRISK, DBOP, and the Sponsor agreed to the modifications as described above. DRISK reviewed the REMS Document and all appended materials submitted on June 8, 2011 and finds the modified REMS acceptable if the following edit is incorporated:

- Revise the REMS Document as follows: See page 3 "v" at the top of the page, immediately above "c. amgen will."

  From: [redacted] (b) (4)

  To: Agree to send a completed signed copy of the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgment Form (or modified version consistent with the allowable changes) to the ESA APPRISE Oncology Program Call Center and retain a copy for my records.

7 REMS Documents and Materials

→ Aranesp and Epogen/Procrit REMS Documents
→ ESA REMS Supporting Document
→ REMS-related materials

148 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Biologic Oncology Products

DBOP REVIEW

RISK EVALUATION AND MITIGATION STRATEGY MODIFICATION REVIEW

BLA/Serial Number:	103951/5173
Drug Name:	Aranesp/darbepoietin alfa
Purpose:	REMS Modification associated with PLR Conversion and Efficacy Supplement
Applicant:	Amgen
Date(s):	Initial submission: 12/26/07, Initial CR: 10/24/08; Resubmission: 10/26/09, 2nd CR: 4/27/10; 2nd resubmission: 3/23/11
Medical Division:	Division of Biological Oncology Products
Reviewer	Jeff Summers, M.D. 6/2/11
Through	Patricia Keegan, M.D., Director Division of Biologic Oncology Products
Review Team:	Pat Keegan, MD; Claudia Karwoski, PharmD, Kaushik Shastri, MD; Amarilys Vega, MD, MPH; Suzanne Robottom, PharmD; Grace Carmouze, Sharon Mills, RN
Project Manager:	Mona Patel, PharmD

DBOP

Risk Evaluation and Mitigation Strategy Modification Review

1 SUMMARY

The purpose of this review is to evaluate the modifications to the Erythropoiesis Stimulating Agents (ESA) Risk Evaluation and Mitigation Strategy (REMS) originally approved February 16, 2010. The changes to the REMS that required a REMS Modification stem from supplement 103951/5173 that was submitted in response to the FDA correspondence dated May 31, 2007, in which FDA requested that Amgen submit a PAS to include revised labeling that addressed the recommendations from the May 10, 2007, Oncologic Drugs Advisory Committee meeting and all data supporting the proposed revisions.

At the time of submission of supplement 103951/5173, the Aranesp labeling did not include a Medication Guide and instead had approved Patient Prescribing Information (PPI). During the protracted course of this submission, a Medication Guide was approved on November 19, 2008 under 103951/5195.

During review of the data from the multiple studies provided and the PLR conversion process, changes were made to the Prescribing Information that entailed changes also be made to the Medication Guide. Since the Medication Guide was now part of a REMS for the ESAs that was approved on February 16, 2010, a REMS modification was required.

Supplement 103951/5173 included proposed draft Prescribing Information provided in the Physician's Labeling Rule (PLR) format. Information and/or data regarding 19 studies was submitted during the review of this supplement. The supplement consisted of the original submission on 12/26/07 and 23 subsequent amendments.

Of particular note, the final Prescribing Information and Medication Guide that will be approved under this supplement will also incorporate changes from a concurrently reviewed and simultaneously approved supplement managed by the Division of Hematology Products (DHP) that addresses the data from the TREAT Study under 103951/5248.

This review will document the changes that were made in the Medication Guide that were specific to the data reviewed under supplement 103951/5173 that was managed by the Division of Biologic Oncology Products and the discussions with DRISK regarding that supplement.

2 INTRODUCTION AND BACKGROUND

The Medication Guide originally approved on November 19, 2008, for Aranesp under 103951/5195 can be found in Appendix 1. The Medication Guide changes included in the second Complete Response Letter of April 27, 2010, that were necessary to accurately reflect the changes in the Prescribing Information based on the clinical review of the data contained in the supplement and the PLR conversion process, can be found in Appendix 2. In addition to the clinical trial data and PLR conversion process entailing changes to the Medication Guide, DRISK also provided a review and comments such that it adhered to current OSE policy regarding Medication Guide content and to improve document readability. Please see the clinical review by Dr. Kaushik Shastri for details on the PLR conversion and efficacy supplement review and the review by Sharon Mills of DRISK regarding the Medication Guide.

During the review of the PLR resubmission of March 23, 2011, it was noted that Amgen had provided submissions to DHP to deregister the SureClick Autoinjector presentation on March 11,

2011 and the Human Serum Albumin (HSA) formulation on May 5, 2011. Since the HSA formulation deregistration also affected the Medication Guide and to avoid the necessity of subsequent REMS modifications, Amgen was requested to include these changes in the PLR submission. These changes also affected multiple other REMS materials; however these changes will be discussed under the REMS modification supplement 103951/5258.

The Medication Guide received on May 20, 2011 that incorporated all of the changes requested by DBOP can be found in Appendix 3. As previously discussed, additional changes to the Prescribing Information and Medication Guide were concurrently being negotiated with Amgen by DHP under a separate submission. The final DRAFT Medication Guide as agreed upon by DHP and Amgen as of the May 31, 2011 e-mail from Ebla Ali Ibrahim can be found in Appendix 4.

3 REVIEW

The following important changes were made to the Medication Guide, each change is not discussed when they are of a similar nature: Please see Appendix 5 for a redlined version that identifies each of the changes made.

Information regarding when a patient should read this Medication Guide contained in the first paragraph was organized into a bulleted format. During the review cycle an additional bullet was added (b) (4) and later deleted as this was not consistent with the recent Federal Register published draft guidance **Medication Guides-Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)** that can be found in Appendix 6.

The Medication Guide Revision Date was deleted. This was initially placed at the beginning of the document with the original approval so that readers could quickly identify whether this represented a new version, and at the end of the document as per DRISK Medication Guide policy. The revision date is now being included only at the end of the document to be consistent with 21CFR §208 that states "The date, identified as such, of the most recent revision of the Medication Guide placed immediately after the last section."

Under **Patients with cancer**

-Information regarding the ESA REMS program and the requirement to sign the patient-healthcare provider acknowledgment form regarding discussions about the risks of taking Aranesp has been included. The Medication Guide was approved prior to the approval of the ESA REMS and had not been updated to include this information.

-The qualifying language regarding experimentally raising hemoglobin beyond the amount needed to avoid red blood cell transfusion was deleted from the primary risk information regarding your tumor growing faster and dieing sooner to increase patient readability. For the same reason language regarding whether these risks exist when Aranesp is given according to FDA approved directions for use was removed.

-Since physicians are not the only individuals licensed to prescribe Aranesp, the term "doctor" was changed to "health care provider" throughout the document except for the last sentence under the section "What are the possible side effects of Aranesp?" that reads "Call your doctor for medical advice about the side effects. You may report side effects to FDA at 1-800-FDA-1088. This language was retained as 21CFR §208 states that for drug products approved under section 505 of the act, the following verbatim statement: "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088" must be included.

-Language was revised to be more patient friendly and patient centered such as including "for you" to personalize the Medication Guide.

-Language was added to improve the grammar and clarify the meaning of certain sentences such as the following revision noted in italics "If you decide to take Aranesp, your healthcare provider should prescribe the smallest dose of Aranesp *that is needed* to lower the chance of getting red blood cell transfusions."

-The bulleted statement under **Patients with cancer** that reads "Aranesp does not improve the symptoms of anemia (lower than normal number of red blood cells), quality of life, fatigue, or well-being for patients with cancer" was placed after the section discussing the circumstances in which Aranesp should not be used for the treatment of anemia. This more closely reflects the Limitations of Use section in the Prescribing Information.

Under **All patients, including patients with cancer or chronic kidney failure**

-The second sentence in the last bullet under symptoms of blood clots was deleted as this was not a symptom.

Under **What is Aranesp**

-The qualifier "for at least two months after starting Aranesp" was included for consistency with the Prescribing Information.

-A section was included to reflect the Limitations of Use section of the Prescribing Information.

Under **Who should not take Aranesp**

-Language has been included for cancer patients that they should not take Aranesp until appropriately counseled by their HCP regarding the risks of Aranesp and signed the ESA REMS required acknowledgement form.

-Language regarding allergies to ingredients in Aranesp has been deleted and clarified to read "Have had a serious allergic reaction to Aranesp" that is consistent with the PI.

-Language regarding pure red cell aplasia (PRCA) as a contraindication has been included to be consistent with the PI.

Under **What should I tell my healthcare provider before taking Aranesp?**

-Information regarding about Amgen's new Pregnancy Surveillance Program has been added.

Under **How should I take Aranesp?**

-Bullet points highlighting the primary components of the REMS requirements have been added.

Under **What are the possible side effects of Aranesp**

The common side effects were revised to reflect the PI.

4 CONCLUSION

This review documents the changes to the Medication Guide that occurred under supplement 103951/5173 as reviewed by the Division of Biologic Oncology Products. The changes to the Medication Guide also required that a REMS modification be submitted. The final approved Medication Guide under this supplement will also include changes resulting from the review of

the TREAT study as conducted by DHP. The Medication Guide agreed upon by DHP and Amgen can be found in Appendix 4 and the details of the additional changes should be sought in the DHP supplement review for the TREAT study under 103951/5248. The REMS modification changes are acceptable and should be approved.

5 Appendices

Appendix 1 Original Medication Guide approved November 19, 2008

MEDICATION GUIDE

Aranesp® (Air-uh-nesp)
(darbepoetin alfa)

Read this Medication Guide before you start Aranesp, each time you refill your prescription, and if you are told by your healthcare provider that there is new information about Aranesp. This Medication Guide was revised August 2008. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Aranesp and ask if there is new information about Aranesp.

What is the most important information I should know about Aranesp?

Using Aranesp can lead to death or other serious side effects.

Patients with cancer:

Your tumor may grow faster and you may die sooner when Aranesp is used experimentally to try to raise your hemoglobin beyond the amount needed to avoid red blood cell transfusion or given to patients who are not getting strong doses of chemotherapy. It is not known whether these risks exist when Aranesp is given according to the FDA-approved directions for use.

You should discuss with your doctor:

- Why Aranesp treatment is being prescribed.
- What are the chances you will get red blood cell transfusions if you do not take Aranesp.
- What are the chances you will get red blood cell transfusions even if you take Aranesp.
- How taking Aranesp may affect the success of your cancer treatment.

If you decide to take Aranesp, your healthcare provider should prescribe the smallest dose of Aranesp to lower the chance of getting red blood cell transfusions.

- After you have finished your chemotherapy course, Aranesp treatment should be stopped.
- Aranesp does not improve the symptoms of anemia (lower than normal number of red blood cells), quality of life, fatigue, or well-being for patients with cancer.

All patients, including patients with cancer or chronic kidney failure:

- You may get serious heart problems such as heart attack, stroke, heart failure, and may die sooner if you are treated with Aranesp to a hemoglobin level above 12 g/dL.
- You may get blood clots at any time while taking Aranesp. If you are receiving Aranesp and you are going to have surgery, talk to your healthcare provider about whether or not you need to take a blood thinner to lessen the chance of blood clots during or following surgery. Clots can form in blood vessels (veins), especially in your leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus).

Call your healthcare provider or get medical help right away if you have any of these symptoms of blood clots:

- Chest pain
- Trouble breathing or shortness of breath

- Pain in your legs, with or without swelling
- A cool or pale arm or leg
- **Sudden confusion, trouble speaking, or trouble understanding others' speech**
- Sudden numbness or weakness in your face, arm, or leg, especially on one side of your body
- Sudden trouble seeing
- Sudden trouble walking, dizziness, loss of balance or coordination
- Loss of consciousness (fainting)
- Hemodialysis vascular access stops working. If you are a patient with chronic kidney failure and have a hemodialysis vascular access, blood clots may form in this access.

Also see "What are the possible side effects of Aranesp?" below.

What is Aranesp?

Aranesp is a man-made form of the protein human erythropoietin that is given to patients to lessen the need for red blood cell transfusions. Aranesp stimulates your bone marrow to make more red blood cells. Having more red blood cells raises your hemoglobin level. If your hemoglobin level stays too high or if your hemoglobin goes up too quickly, this may lead to serious health problems which may result in death. These serious health problems may happen even if you take Aranesp and do not have an increase in your hemoglobin level.

Aranesp may be used to treat a lower than normal number of red blood cells (anemia) if it is caused by:

- Chronic kidney failure (you may or may not be on dialysis)
- Chemotherapy that is used to treat some types of cancer

Who should not take Aranesp?

Do not take Aranesp if you:

- Have high blood pressure that is not controlled (uncontrolled hypertension).
- Have allergies to any of the ingredients in Aranesp. See the end of this Medication Guide for a complete list of ingredients in Aranesp.

What should I tell my healthcare provider before taking Aranesp?

Aranesp may not be right for you. **Tell your healthcare provider about all your health conditions,** including if you:

- Have heart disease.
- Have high blood pressure.
- Have had a seizure (convulsion) or stroke.
- Are pregnant or planning to become pregnant. It is not known if Aranesp will harm your unborn baby.
- Are breast-feeding or planning to breast-feed. It is not known if Aranesp passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How should I take Aranesp?

- **Continue to follow your healthcare provider's instructions for diet, dialysis, and medicines, including** medicines for high blood pressure, while taking Aranesp.
- Have your blood pressure checked as instructed by your healthcare provider.
- If you or your caregiver has been trained to give Aranesp shots (injections) at home:

- Be sure that you read, understand, and follow the "Patient Instructions for Use" that come with Aranesp.
- Take Aranesp exactly as your healthcare provider tells you to. Do not change the dose of Aranesp unless told to do so by your healthcare provider.
- Your healthcare provider will show you how much Aranesp to use, how to inject it, how often it should be injected, and how to safely throw away the used vial, syringes, and needles.
- If you miss a dose of Aranesp, call your healthcare provider right away and ask what to do.
- If you take more than the prescribed amount of Aranesp, call your healthcare provider right away.

What are the possible side effects of Aranesp?

Aranesp may cause serious side effects. See **"What is the most important information I should know about Aranesp?"**

Other side effects of Aranesp, which may also be serious, include:

- **High blood pressure in patients with chronic kidney failure.** Your blood pressure may go up or be difficult to control with blood pressure medicine while taking Aranesp. This can happen even if you have never had high blood pressure before. Your healthcare provider should check your blood pressure often. If your blood pressure does go up, your healthcare provider may prescribe new or more blood pressure medicine.

- **Seizures.** If you have any seizures while taking Aranesp, get medical help right away and tell your healthcare provider.

- **Antibodies to Aranesp.** Your body may make antibodies to Aranesp. These antibodies can block or lessen your body's ability to make red blood cells and cause you to have severe anemia. Call your healthcare provider if you have unusual tiredness, lack of energy, dizziness, or fainting. You may need to stop taking Aranesp.

- **Serious allergic reactions.** Serious allergic reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness and fainting because of a drop in blood pressure, swelling around your mouth or eyes, fast pulse, or sweating. If you have a serious allergic reaction, stop using Aranesp and call your healthcare provider or get medical help right away.

The needle cover on the prefilled syringe contains a material that is like latex. If you know you are allergic to latex, talk to your healthcare provider before using Aranesp.

Common side effects of Aranesp include:

- Swelling in cancer patients
- Rash
- Injection site pain

These are not all of the possible side effects of Aranesp. Your healthcare provider can give you a more complete list. Tell your healthcare provider about any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Aranesp?

- Do not shake Aranesp.
- Protect Aranesp from light.
- Store Aranesp in the refrigerator between 36°F to 46°F (2°C to 8°C).
- **Do not freeze.** Do not use Aranesp that has been frozen.

Keep Aranesp and all medicines out of the reach of children.

General information about Aranesp

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use Aranesp only for the condition for which it has been prescribed. Do not give Aranesp to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Aranesp. If you would like more information about Aranesp, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Aranesp that is written for healthcare professionals. For more information, go to the following website: www.aranesp.com or call 1-800-77-AMGEN.

What are the ingredients in Aranesp?

Active Ingredient: darbepoetin alfa

Inactive Ingredients:

- polysorbate solution: polysorbate 80, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and sodium chloride in Water for injection, USP.
- albumin solution: albumin (human), sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and sodium chloride in Water for Injection, USP.

Revised: 08/2008

This Medication Guide has been approved by the U.S. Food and Drug Administration.

AMGEN®

Manufactured by:

Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

1xxxxxx - v1

20 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

Date: May 9, 2011

To: Patricia Keegan, MD, Director
Division of Biologic Oncology Products

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management

From: Amarilys Vega, MD, MPH Amarilys Vega 6/10/2011
Risk Management Analyst
Division of Risk Management

Kate Heinrich Oswell, MA
Health Education Reviewer
Division of Risk Management

Suzanne Robottom, PharmD, Team Leader
Division of Risk Management
6/10/11

Subject: Erythropoiesis Stimulating Agents (ESAs)
Proposed REMS Modifications Review (1)

Drug Name (Established Name): Aranesp (darbepoetin alfa)
Epogen (epoetin alfa)
Procrit (epoetin alfa)

Application Type/Number: BLA 103951/5258
BLA 103234/5266
BLA 103951/5173
BLA 103234/5166

Applicant: **Amgen**

OSE RCM #: 2010-550

TSI #: 242

Table of Content

1 Introduction

The purpose of this review is to evaluate the applicant's modifications to the Erythropoiesis Stimulating Agents (ESAs including Aranesp®, Epogen®, and Procrit®) Risk Evaluation and Mitigation Strategy (REMS) submitted to the FDA in March 22, 2011. These revisions have been under discussion with the applicant since mid-October 2010 and involve changes to allow for electronic signature and storage of the Patient Acknowledgement Form. These modifications are being reviewed to align with additional changes resulting from the conversion of the current label to PLR format and safety labeling changes to incorporate new safety information from the TREAT study.

This interim review provides recommendations on the applicant's proposed ESA REMS modifications. This review includes letter-ready comments for the applicant.

These are preliminary comments. The Division of Biologic Oncology Products (DBOP) and the applicant should anticipate additional comments as the submission undergoes further review. We note that additional revisions to the appended REMS materials will need to be made once the label is finalized (inclusion of the TREAT study results and PLR conversion).

2 Materials Reviewed

DRISK reviewed the following

- Amgen ESA REMS modifications submitted March 22 and 23, 2011, Sequence No. 0351, containing the Applicant's final response to FDA comments dated December 29, 2010.
- Amgen submission dated January 18, 2011, Sequence No. 0344, including the Applicant's interim response to FDA comments dated December 29, 2010 (related to the October 14, 2011 submission).
- DRISK Interim REMS Modification Review Comments dated December 20, 2010.

In addition, DRISK reviewed the electronic document room for REMS-related submissions between October 2010 to present and note the following submissions that are related to these modifications and have been addressed by the December 20, 2010 DRISK review:

- REMS modification submitted October 14, 2011 - (0386 → 103951/5258.0) - 1st REMS assessment AND proposed REMS modifications
- REMS modification submitted December 8, 2011 (this was in response to request from FDA)

The following submissions are REMS-related but are not pertinent to the subject of this review:

- REMS modification submitted October 14, 2011 (b) (4) → addressed by DRISK Assessment Team
- December 3, 2010 -- "RTQ and Utilization Assessment" -- pilot programs, etc. → no action by RMA; addressed by OSE Division of Epidemiology
- February 16, 2011 -- 2nd REMS assessment → This submission is addressed under separate cover

3 Background

In December 29, 2010 the FDA sent comments to Amgen regarding their proposed ESAs REMS modifications. The Applicant submitted an interim response to the Agency's comments in January 18, 2011 indicating that some of the revisions would be incorporated in a subsequent submission. In March 3, 2011, FDA requested Amgen to send a formal submission of all proposed REMS modifications. Amgen submitted all REMS-related materials addressing FDA comments from December 29, 2010 in March 22, 2011.

This review evaluates Amgen's January 18, 2011 and March 22, 2011 submissions of the ESAs REMS modifications.

4 ESA REMS Modifications Proposed by the Sponsor

The following sections include DRISK evaluation of Amgen's response to FDA comments dated December 29, 2010.

4.1 Agency Comment 1 (December 29, 2010)

All of the proposed revisions to the website are acceptable with the exception of the proposal to [redacted (b) (4)] The safety information applies to the risk addressed through the REMS and any changes to this information would likely have an impact on the REMS regardless [redacted (b) (4)].

Amgen Response 1 *(January 18, 2011)*

Amgen and Centocor Ortho Biotech Inc. (COBI) appreciate FDA's acceptance of all but one of the proposed website revisions. Revised website screenshots that [redacted (b) (4)] are enclosed; the revision is also incorporated into the proposed final REMS.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

"Important Safety Information": Upon further consideration, we agree with deleting of the [redacted (b) (4)] ***from all webpages contingent upon modification of the ESAs Apprise Oncology Program homepage. On the homepage, include a description of the risks associated to ESAs exposure in the body of the page (see below). In addition,*** [redacted (b) (4)] ***and create a "tab" in the header section to include the risk information addressed through the REMS. Please note that the risk information will need to be consistent with the final agreed upon label.***

Following are suggested modifications to the webpage

What is the ESA APPRISE Oncology Program?

Erythropoiesis Stimulating Agents (ESAs) include Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), and Procrit® (epoetin alfa)]. The FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the decision to initiate treatment with an ESA is informed by a discussion between the patient and healthcare provider (HCP) about the benefits and risks associated with ESA therapy.

[redacted (b) (4)]

What are risks addressed through the ESA APPRISE Oncology Program?

- (b) (4)
    - ESAs shortened overall survival and/or increase the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- **Increased risk of death from cardiovascular and thromboembolic reactions** in clinical studies in patients with cancer treated ESAs

Key Program Requirements

(b) (4)

The ESA APPRISE Oncology Program training and enrollment takes you step-by-step through the required training and enrollment process.

Failure to comply with the ESA APPRISE Oncology Program requirements will result in suspension of your access to ESAs

Appropriate Use of ESAs for Patients with Cancer

- ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- ESAs are **NOT Indicated** for use
    - in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy;
    - (b) (4)
    - as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- ESAs have not been shown to improve quality of life, fatigue, or patient well-being.

Important Dosing and Treatment Information

- Initiate ESA therapy in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL
    - Use the lowest dose needed to avoid red blood cell (RBC) transfusions
    - Discontinue ESA treatment following completion of a chemotherapy course.

Questions about the ESA APPRISE Oncology Program?

If you need more information about the ESA APPRISE Oncology Program:

- Contact your local Amgen or Centocor Ortho Biotech Products Field Representative; or
- Call the ESA APPRISE Oncology Program Call Center at 1-866-284-8089

*Additional information on REMS may be found at www.FDA.gov

4.2 Agency Question 2 (December 29, 2010)

The plan to disseminate the flashcard to communicate these changes to HCPs and Hospital Designees is an acceptable short-term, interim solution.

a. Submit the letter that will accompany the flashcard for review.

Amgen Response *(January 18, 2011)*

The original proposal by Amgen and COBI stated that the flashcard would be mailed out with a letter to all currently enrolled HCPs and Hospital Designees, included on the outside of all HCP Program Starter Kits sent to newly enrolled HCPs and Hospital Designees, and communicated via field representatives. Instead of being mailed as a hardcopy to enrolled HCPs and Hospital Designees, the flashcard will be sent via email with the following email text:

(b) (4)

In addition, the flashcard will be available on the Forms & Resources page of the ESA APPRISE Oncology Program Website as shown on the enclosed revised website screenshots.

In order to inform prescribers and hospital designees about the availability of these changes to the REMS in an expedited manner, the Companies request FDA agreement that we can implement the flashcard as soon as possible, even if formal written approval of this supplement has not been provided.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

In the January 18, 2011 response to FDA comments, Amgen included a copy of the email they intended to send to all enrolled HCPs and Hospital Designees regarding the flashcard.

DRISK reviewed the proposed communication and considers it acceptable.

Amgen requested FDA agreement to implement the flashcard as soon as possible, even before the formal written approval of the supplement. The FDA agreed to this proposal and the flashcard is currently available in the website under the "Forms & Resources" tab.

4.3 Agency Question 3 (December 29, 2010)

The long-term modification should include revisions to the REMS materials. Revise the "Training Module for Hospital Designees" and "Training Module for Healthcare Providers" and corresponding "overview" flashcards, as appropriate, to communicate these changes. These changes should be incorporated before the next scheduled printing of the REMS materials. The website should be updated at the time the REMS modifications are approved and/or the materials are revised. The flashcard should be used until the revised training materials are fully implemented.

a. Submit the revised training materials for review.

b. Provide the date when you anticipate the REMS materials will be re-printed.

c. Specify the time the flashcard will remain on the website after the training modules are updated on the website and how long you intend to over-wrap the starter kits.

d. On the website, identify the link to the flashcard as "new" or "program update" or some other mechanism to draw attention that this is an important change.

Amgen Response *(January 18, 2011)*

a. Amgen and COBI will submit all revised REMS materials for FDA review. To minimize the number of REMS modification supplements requiring FDA review, the Companies propose to submit the long-term changes related to the agreed-upon Patient and Healthcare Professional Acknowledgement Form (PAF) flexibility in a prior approval supplement together with the additional REMS changes related to the PLR conversion (eg, change in the oncology indication statement).

b. REMS materials will be re-printed as soon as possible after the finalization of the REMS modification supplement described in the response to FDA question 3a. In the meantime, the Companies will communicate the allowable changes to the PAF as described in the response to FDA question 2 above.

c. It will be beneficial for the information on the flashcard to be readily available on an ongoing basis from a variety of sources. Therefore, Amgen and COBI will continue to use the flashcard as a REMS tool when the long-term modifications to the REMS are complete. The flashcard will remain on the website after the relevant information has been incorporated into the training modules and any other REMS materials as appropriate. As part of the long-term changes, the starter kits will also be modified so that the PAF flashcard is a listed enclosure.

d. The website home page and the Forms & Resources page (in the proposed final REMS) have been updated to draw attention that the PAF flashcard is an important addition. See also the enclosed revised website screenshots.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

a. Amgen and COBI submitted all revised REMS materials in March 22, 2011.

b. The sponsors stated in their response that REMS materials will be re-printed as soon as possible after the finalization of the REMS modification supplement. DRISK find the proposed approach acceptable.

c. The Sponsors plan to make the information on the flashcard available from the website and starter kit even after all the modifications are incorporated into all relevant REMS materials. DRISK find the proposed approach acceptable.

d. The website home page and the Forms & Resources page were updated to highlight changes to the Patient Acknowledgement Form.

4.4 Agency Question 4 (December 29, 2010)

As part of the long-term modification, revise the Patient and Healthcare Professional Acknowledgement Form to explain that the form may be submitted or maintained in a modified format consistent with the allowable changes and archived as hard copy or electronically; accessible in a manner that does not disclose a patient's complete medical record. For example, the following revisions could be incorporated into the Acknowledgment Form:

a. under "in private practice clinics"

Include "Fax the completed form *(or modified version consistent with the allowable changes)* to the ESA APPRISE Oncology Call Center at 1-866-553-8124 or mail a copy using a prepaid envelope to...."

Delete [redacted] (b) (4)

and replace with

"Keep a record of the signed Acknowledgment. The Acknowledgment must be available to the ESA APPRISE Oncology Program for monitoring/auditing purposes in a manner that does not require disclosure of the patient's medical record."

b. under "in hospitals"

Include "Provide the completed form (or modified version with allowable changes) to the hospital designee responsible for maintaining and storing the forms [redacted] (b) (4)

As part of the long-term modification, revision to the Patient and Healthcare Professional Acknowledgement Form that explains that the form may be submitted or maintained in a modified format consistent with the allowable changes and archived as hard copy or electronically, accessible in a manner that does not disclose a patient's complete medical record, will be submitted for FDA review as described in the response to FDA question 3a above.

Amgen Response *(January 18, 2011)*

As part of the long-term modification, revision to the Patient and Healthcare Professional Acknowledgement Form that explains that the form may be submitted or maintained in a modified format consistent with the allowable changes and archived as hard copy or electronically, accessible in a manner that does not disclose a patient's complete medical record, will be submitted for FDA review as described in the response to FDA question 3a above.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

In compliance to FDA's request, the Sponsors added the following parenthetical statement to communicate the acceptability of modified versions of the Acknowledgement Form: "(or modified version consistent with the allowable changes)". The clarifying statement was inserted into relevant places in the following documents:

- ***REMS concise document***
- ***REMS supporting document***
- ***REMS website screen shots***
- ***ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers***
- ***Training Module for Healthcare Providers***
- ***ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form (Acknowledgment Form)***
- ***HCP Program Starter Kit***

- *Training Module for Hospital Designees*

The Sponsor modified the ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form to include the following text:

In private-practice clinics

> ***… Keep a record of the signed Acknowledgment Form. The Acknowledgment Form must be available to the ESA APPRISE Oncology Program for monitoring/auditing purposes in a manner that does not require disclosure of the patient's medical record.***

In hospitals

> ***Provide the completed form (or modified version consistent with the allowable changes) to the hospital designee responsible for maintaining and storing the forms or the forms may be archived electronically through an electronic medical record system as long as they are retrievable.***

DRISK finds the proposed revisions acceptable.

In addition, to highlight the availability of the "Guidelines for Patient Acknowledgement Form Integration with Healthcare Systems and Clinics", DRISK recommends the following modifications:

a. Training Module for Healthcare Providers and Training Module for Hospital Designees, section 3 Program Requirements and Materials for Healthcare Providers (and Hospital Designees): replace the sentence (b) (4) ***' with the following one, "To learn more about allowed changes to the Patient Acknowledgment Form, please refer to the Guidelines for Patient Acknowledgment Form Integration with in Healthcare Systems and Clinics flashcard". Please hyperlink the text to the flashcard.***

4.5 Agency Question 5 (December 29, 2010)

a. The following comments are in response to the proposed Concise REMS Document you provided on December 8, 2010

   i. Revise the Proposed REMS Concise Document to include the new underscored and italicized language as identified, and the deletions described as follows: Delete reference to the (b) (4) under section II C 4 "Aranesp/Epogen/Procrit will be dispensed to patients with cancer with evidence or other documentation of safe use conditions under 505-1(f)(3)(D)"

   ii. Page 5, section II C 1 c iv "I will send a signed copy of the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgment form (or modified version with allowable changes) back to the ESA APPRISE Oncology Program Call Center."

   iii. Page 8, section II C 2 c v (b) (4)

   iv. Page 11, section II D "Implementation System"

- Add the following new section 1.a

(b) (4)

i. Removal of title instruction and footnoted text

ii. (b) (4)

iii.

The content in the Patient Acknowledgement and Healthcare Professional sections of the form cannot be changed. No content can be added or removed from these sections.

(b) (4)

- Continue with the old section 1.a as 1.b

"The ESA APPRISE Oncology Program Center will conduct monitoring of all private practice..."

iv. Revise the header date to Month/Year consistent with the REMS modification approval

b. Please note that the REMS Concise Document can not include any appended materials that were not approved with the REMS. The final REMS submission before approval of these modifications must include all (revised) REMS materials appended to the REMS.

Amgen Response *(January 18, 2011)*

a. Changes i and iv have been incorporated into the concise document (redline and clean) enclosed for FDA review. The changes requested by FDA under ii and iii will result in inconsistencies between the concise REMS documents and several appended materials. (b) (4) With respect to v, because the REMS modification is not yet approved, the header date has been changed to January 2011 in anticipation that the supplement will be approved this month.

b. All appended materials listed in the concise REMS have been submitted for FDA review and approval. The proposed final REMS (concise and appended materials) is enclosed.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

a. The Sponsor reasonably addressed in the REMS concise document all the modifications specified by the FDA in the March 29, 2010 document.

b. The March 22, 2011 submission of the final REMS included all revised REMS materials and a single document containing the entire final clean version of the REMS with all REMS components appended.

4.6 Agency Question 6 (December 29, 2010)

Revise the REMS Supporting Document to be consistent with all changes made to the REMS document.

Amgen Response *(January 18, 2011)*

A revised REMS Supporting Document (dated 7 January 2011, redline and clean) is enclosed.

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

DRISK finds the proposed revisions acceptable.

4.7 Agency Question 7 (December 29, 2010)

Resubmission Requirements and Instructions: Submit the revised proposed REMS with all attached or appended materials and the REMS Supporting Document in the following formats:

a. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents.

b. Submit the REMS and the REMS Supporting Document as two separate WORD documents. The entire REMS document (Concise REMS and all appended materials) should be in a single WORD document.

c. If certain documents such as enrollment form are only in PDF format, they may be submitted as such, with changes noted using PDF mark-up tools.

Amgen Response *(January 18, 2011)*

a. The following revised documents are submitted in WORD:

   • *Concise REMS (redline and clean)*

   • *REMS Supporting Document (redline and clean)*

b. The concise REMS and the REMS Supporting Document are enclosed as separate WORD documents. Because many of the appended materials are in PDF format, it is not possible to submit the entire REMS document in Word. A PDF document providing clean versions of the proposed final REMS (concise REMS and all appended materials as listed below) is enclosed.

Proposed Final REMS Components	Version / Date
Concise REMS (product specific)	January 2011
Medication Guide (product specific)	February 16, 2010
(b) (4)	February 16, 2010
Dear Healthcare Provider (DHCP) Letter to HCPs who may purchase or prescribe ESAs for patients with cancer	February 16, 2010
Dear Healthcare Provider (DHCP) Letter to hospital Directors of Pharmacy/Administrators	February 16, 2010

Proposed Final REMS Components	Version / Date
(b) (4)	February 16, 2010
ESA APPRISE Oncology Program Website	January 2011
ESA REMS flashcard	February 16, 2010
ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers	February 16, 2010
ESA APPRISE Oncology Program Training Module for Healthcare Providers	February 16, 2010
ESA APPRISE Oncology Program Healthcare Provider Flashcard	February 16, 2010
ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form	Version 2, 5/10
HCP Program Starter Kit	February 16, 2010
ESA APPRISE Oncology Program Enrollment Form for Hospitals	Version 2, 01/11
ESA APPRISE Oncology Program Training Module for Hospital Designees	February 16, 2010
ESA APPRISE Oncology Program Hospital Process Overview Flashcard	February 16, 2010
Guidelines for Patient Acknowledgement Form Integration within Healthcare Systems and Clinics	January 2011

c. Annotated versions of the following revised documents are enclosed, with changes noted using PDF mark-up tools. In addition, a clean version of the entire final REMS (concise REMS and all appended materials) in PDF format are enclosed as listed in the response to FDA question 7b.

Document	Description of Proposed Modification and Rationale
Hospital Designee Enrollment Form (redline)	Modification: Removal of (b) (4) (b) (4) and replacement with Customer ID Type and # number issued by the Companies. Rationale (b) (4) The Customer ID number(s) issued by the Companies is more likely to be known by the hospital designee, or can easily be obtained from a company field representative at the time of training and enrollment. The addition of the Customer ID# will assist the ESA APPRISE Oncology Program administrator in confirmation of the identity of the hospital entered on the manual enrollment form. This proposal has been further modified to enable clarification of which ID number is inserted, as in some case a hospital could be assigned more than one Customer ID#. This minor change will not require re-enrollment of hospital designees nor otherwise impact existing enrollments.

Document	Description of Proposed Modification and Rationale
Revised Website Screenshots	
(b) (4) illustrated by the annotated Home Page)	Rationale: Retaining these items from the current approved website per FDA request
Home Page	Modification: Addition of "New PAF Modification Guidelines" to the Access forms & resources" button Rationale: Highlights this important addition
Forms & Resources	Modification: Addition of link to PAF modification guidelines flashcard Rationale: Highlights this important addition

DRISK Comments on Amgen's submissions in January 18, 2011 and March 22, 2011

The March 22, 2011 submission includes all the REMS-related documents required to complete DRISK review.

5 Additional Recommendations Regarding the March 22, 2011 Submission

5.1 Enrollment Forms for HCPs and Hospital Designees

Bullets 1 and 2 of the Enrollment Form for HCPs/Hospital Designees should be consistent with the label (boxed warning). Please note that the text is subject to change to be consistent with the final agreed upon labeling. For example, based on the current draft, we recommend the following:

By completing this form, I agree to the following:

- I have reviewed the appropriate current prescribing information for Aranesp® or Epogen®/Procrit®.
  - I understand that ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in (b) (4) clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers
  - I understand that ESAs increased the risk of death from cardiovascular and thromboembolic reactions in clinical studies in patients with cancer treated with ESAs
  - (b) (4)

5.2 Changes to the HCP Training Module

Revise the Traning Module (sections 1 and 2) to be consisent with the final agreed upon label. In addition, section 2 should be revised as follows:

Appropriate Use of ESAs for Patients With Cancer

- ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- ESAs are **NOT indicated** for use

- in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- (b) (4)
- as a substitute for RBC transfusions in patients who require immediate correction of anemia.

- ESAs have not been shown to improve quality of life, fatigue, or patient well-being.

Important Dosing and Treatment Information

- Initiate ESAs in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL.
- Use the lowest dose of ESAs necessary to avoid RBC transfusions.
- Discontinue ESAs following the completion of a chemotherapy course.

Please see the full prescribing information for Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), or Procrit® (epoetin alfa) for other risks associated with these ESAs, including other Warnings and Precautions, and Adverse Reactions.

Please see the full Prescribing Information for Procrit® regarding the pediatric use of Procrit®. The safety and efficacy of Aranesp® in pediatric cancer patients have not been established.

5.3 Errors in the March 22, 2011 Submission

The following errors were identified in the March 22, 2011 submission,

5.3.1 Website: Training and Enrollment for Hospitals tab main page:

- The following sentence should be deleted (b) (4)

5.3.2 Website: ESA APPRISE Oncology Program Enrollment for Hospitals tab:

- Third bullet from the top, Epogen®/Procrit®[INSERT SPACE]to patients
- Edit the following sentence as follows, "I have completed the ESA APPRISE Training Module. I understand that failure to comply with the ESA APPRISE Oncology Program requirements will result in suspension of my hospital's access to ESAs".

5.3.3 Website: Training & Enrollment tab

- Pop-up window that appears when answering "YES" to the question, "Please confirm your enrollment in this program is related to the treatment of patients with cancer" has the option, "For non-prescribing HCPs—Training only". This option does not belong in this window but should be provided in the pop-up window resulting from answering "NO" to the question, "Please confirm your enrollment in this program is related to the treatment of patients with cancer".

5.4 Additional Recommendations to Improve Readability

We recommend the following revisions to improve readability:

5.4.1 ESA APPRISE Oncology Program Emphasis on REMS Document Materials (b) (4) Dear HCP, Dear Hospital Administrator, Director of Pharmacy, and Dear [insert organization name] letters' header and footer: move ESA APPRISE Oncology Program logo and text in the right side of footer to the header (left or right side). Move the names and logos of the sponsors to the footer. Alternatively, place both companies' names and logos on opposite side of the ESA APPRISE Oncology Program logo in the header. Format the text in the footer to

resemble the format used in the footer of the Guidelines for Patient Acknowledgment Form Integration flashcard.

5.4.2 Website screenshots

Overall, avoid using Healthcare Providers (HCPs) in section headings, enrollment form titles, and in section review verification questions.

5.4.3 Training and Enrollment for HCPs tab main page

Abbreviate heading to "ESA APPRISE Training Module for Health Care Providers". Include the additional information that is currently part of the title in the body of the page. For example, add the following sentence or like after the first paragraph, "This training module is intended for HCPs who prescribe or prescribe and dispense ESAs for patients with cancer".

5.4.4 Training and Enrollment for HCPs tab Section 3

Fourth bullet can be simplified; replace with the following: " Document that the risk:benefit discussion with the patient has occurred by completing and signing the ESA APPRISE Oncology Program Patient and Healthcare Provider (HCP) Acknowledgement Form".

5.4.5 Training and Enrollment for Hospitals tab main page:

Abbreviate heading to "ESA APPRISE Training Module for Hospital Designees". Include the additional information in the body of the page. For example, add the following sentence or like after the first paragraph, "This training module is intended for Hospital Designees at hospitals that dispense ESAs for patients with cancer".

5.4.6 Training and Enrollment for Hospitals tab Section 3

Fourth bullet can be simplified; replace with the following: " Document that the risk:benefit discussion with the patient has occurred by completing and signing the ESA APPRISE Oncology Program Patient and Healthcare Provider (HCP) Acknowledgement Form".

Third bullet under Hospital Designee Requirements, use HCPs abbreviation only.

6 Recommendations for the DBOP

DRISK finds that the Applicant's submission of March 22, 2011 includes all REMS materials as requested by the FDA and that all REMS materials were revised as per the comments provided to the sponsors by FDA December 29, 2011 with a few exceptions for which the sponsor provided a reasonable explanation and offered an acceptable alternative approach.

DRISK requests you convey the following recommendations to Amgen:

6.1 Important Safety Information

Upon further consideration, we agree with deleting of the (b) (4) from all webpages contingent upon modification of the ESAs Apprise Oncology Program homepage. On the homepage, include a description of the risks associated to ESAs exposure in the body of the page (see below).

What is the ESA APPRISE Oncology Program?

Erythropoiesis Stimulating Agents (ESAs) include Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), and Procrit® (epoetin alfa)]. The FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the decision to initiate treatment with an ESA is informed by a discussion between the patient and healthcare provider (HCP) about the benefits and risks associated with ESA therapy.

(b) (4)

[redacted]

What are risks addressed through the ESA APPRISE Oncology Program?

- (b) (4)
  - ESAs shortened overall survival and/or increase the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- **Increased risk of death from cardiovascular and thromboembolic reactions in clinical studies in patients with cancer treated ESAs**

Key Program Requirements

(b) (4)

[redacted]

The ESA APPRISE Oncology Program training and enrollment takes you step-by-step through the required training and enrollment process.

Failure to comply with the ESA APPRISE Oncology Program requirements will result in suspension of your access to ESAs

Appropriate Use of ESAs for Patients with Cancer

- ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- ESAs are **NOT** Indicated for use
  - in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy;
  - (b) (4)
  - as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- ESAs have not been shown to improve quality of life, fatigue, or patient well-being.

Important Dosing and Treatment Information

- Initiate ESA therapy in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL
  - Use the lowest dose needed to avoid red blood cell (RBC) transfusions
  - Discontinue ESA treatment following completion of a chemotherapy course.

Questions about the ESA APPRISE Oncology Program?

If you need more information about the ESA APPRISE Oncology Program:

- Contact your local Amgen or Centocor Ortho Biotech Products Field Representative, or
- Call the ESA APPRISE Oncology Program Call Center at 1-866-284-8089

*Additional information on REMS may be found at www.FDA.gov

In addition, [redacted] create a "tab" in the header section to include the risk information addressed through the REMS. Please note that the risk information will need to be consistent with the final agreed upon label.

6.2 Allowable Changes to Patient Acknowledgement Form

We consider that, after the incorporation of the information regarding the changes allowed to the Patient Acknowledgement Form into all relevant REMS materials, it is acceptable to have the Guidelines for Patient Acknowledgement Form Integration within Healthcare Systems and Clinics flashcard available at the program website and through the Starter Kit. In addition, to highlight the availability of the "Guidelines for Patient Acknowledgement Form Integration with Healthcare Systems and Clinics", we recommend the following modification to the Training Module for Healthcare Providers and Training Module for Hospital Designees, section 3 Program Requirements and Materials for Healthcare Providers (and Hospital Designees): replace the sentence [redacted] with the following one, "To learn more about allowed changes to the Patient Acknowledgment Form, please refer to the Guidelines for Patient Acknowledgment Form Integration with in Healthcare Systems and Clinics flashcard". A hyperlink to the flashcard should be also included.

6.3 Enrollment Forms for HCPs and Hospital Designees

Bullets 1 and 2 of the Enrollment Form for HCPs/Hospital Designees should be consistent with the label (boxed warning). Please note that the text is subject to change to be consistent with the final agreed upon labeling. For example, based on the current draft, we recommend the following:

By completing this form, I agree to the following:

- I have reviewed the appropriate current prescribing information for Aranesp® or Epogen®/Procrit®.
  - I understand that ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in [redacted] clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers
  - I understand that ESAs increased the risk of death from cardiovascular and thromboembolic reactions in clinical studies in patients with cancer treated with ESAs
  - [redacted].

6.4 HCP Training Module

Revise the HCP Traning Module (sections 1 and 2) to be consisent with the final agreed upon label. In addition, section 2 should be revised as follows:

Appropriate Use of ESAs for Patients With Cancer

- ESAs are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- ESAs are **NOT** indicated for use
  - in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
  - [redacted]
  - as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- ESAs have not been shown to improve quality of life, fatigue, or patient well-being.

Important Dosing and Treatment Information

- Initiate ESAs in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/dL.
- Use the lowest dose of ESAs necessary to avoid RBC transfusions.
- Discontinue ESAs following the completion of a chemotherapy course.

Please see the full prescribing information for Aranesp® (darbepoetin alfa), Epogen® (epoetin alfa), or Procrit® (epoetin alfa) for other risks associated with these ESAs, including other Warnings and Precautions, and Adverse Reactions.

Please see the full Prescribing Information for Procrit® regarding the pediatric use of Procrit®. The safety and efficacy of Aranesp® in pediatric cancer patients have not been established.

6.5 Reprinting Materials

The sponsors stated in their response that REMS materials will be re-printed as soon as possible after the finalization of the REMS modification supplement. This proposed approach acceptable.

6.6 Corrections

We recommend correction of the following errors in the REMS materials:

6.6.1 Website: Training and Enrollment for Hospitals tab main page:
The following sentence should be deleted since it only applies to HCPs and not to hospital designees, (b) (4)

6.6.2 Website: ESA APPRISE Oncology Program Enrollment for Hospitals tab
Third bullet from the top, Epogen®/Procrit®[INSERT SPACE]to patients

Edit the following sentence as follows, "I have completed the ESA APPRISE Training Module. I understand that failure to comply with the ESA APPRISE Oncology Program requirements will result in suspension of *my hospital's* access to ESAs".

6.6.3 Website: Training & Enrollment tab
Pop-up window that appears when answering "YES" to the question, "Please confirm your enrollment in this program is related to the treatment of patients with cancer" has the option, "For non-prescribing HCPs—Training only". This option does not belong in this window but should be provided in the pop-up window resulting from answering "NO" to the question, "Please confirm your enrollment in this program is related to the treatment of patients with cancer".

6.7 Additional recommendations to improve readability

We recommend the following revisions to improve readability

6.7.1 (b) (4) Dear HCP, Dear Hospital Administrator, Director of Pharmacy, and Dear [insert organization name] letters' header and footer: move ESA APPRISE Oncology Program logo and text in the right side of footer to the header (left or right side). Move the names and logos of the sponsors to the footer. Alternatively, place both companies' names and logos on opposite side of the ESA APPRISE Oncology Program logo in the header. Format the text in the footer to resemble the format used in the footer of the Guidelines for Patient Acknowledgment Form Integration flashcard.

6.7.2 Website screenshots

- Overall, avoid using Healthcare Providers (HCPs) in section headings, enrollment form titles, and in section review verification questions.

- Training and Enrollment for HCPs tab main page
  Abbreviate heading to "ESA APPRISE Training Module for Health Care Providers". Include the additional information that is currently part of the title in the body of the page. For example, add the following sentence or like after the first paragraph, "This training module is intended for HCPs who prescribe or prescribe and dispense ESAs for patients with cancer".

- Training and Enrollment for HCPs tab Section 3
  Fourth bullet can be simplified; replace with the following: " Document that the risk:benefit discussion with the patient has occurred by completing and signing the ESA APPRISE Oncology Program Patient and Healthcare Provider (HCP) Acknowledgement Form".

- Training and Enrollment for Hospitals tab main page
  Abbreviate heading to "ESA APPRISE Training Module for Hospital Designees". Include the additional information in the body of the page. For example, add the following sentence or like after the first paragraph, "This training module is intended for Hospital Designees at hospitals that dispense ESAs for patients with cancer".

- Training and Enrollment for Hospitals tab Section 3
  Fourth bullet can be simplified; replace with the following: " Document that the risk:benefit discussion with the patient has occurred by completing and signing the ESA APPRISE Oncology Program Patient and Healthcare Provider (HCP) Acknowledgement Form".

  Third bullet under Hospital Designee Requirements, use HCPs abbreviation only.