

**BL 103951 ARANESP® (DARBEPOETIN ALFA)**

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**PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)****I. GOALS**

- A. 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.
- B. 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 decreased survival and/or poorer tumor outcomes.

**II. REMS ELEMENTS****A. Medication Guides will be provided in accordance with 21 CFR Part 208**

The Medication Guide will be provided as follows:

- **Retail or Hospital Outpatient Pharmacy Services**
  - With every dispensing pack of Aranesp
  - In a printable format that can be downloaded from the aranesp.com website or by contacting Amgen via their company Medical Information Department toll-free number.
- **Physician Offices/Clinics/Hospital Inpatient and In-Clinic Services/Dialysis Centers/**
  - Physician offices, clinics, hospital inpatient pharmacies, and in-clinic services/dialysis centers will provide a Medication Guide to each patient or the patient's representative when the product is dispensed for as long as the treatment continues.
  - Amgen will ensure that a sufficient quantity of Medication Guides are made available to physician offices, clinics, hospital inpatient pharmacies, and in-clinic services/dialysis centers that administer Aranesp to provide to the patient or the patient's representative when the product is dispensed.
  - Medication Guides will also be made available to these settings through field-based personnel upon request, in a printable format that can be

downloaded from the aranesp.com website, or by contacting Amgen via their company Medical Information Department toll-free number.

- Amgen will ensure that HCPs, clinics, and hospitals are notified and provided with updated Aranesp Medication Guides if they are materially revised.
- **Additionally, as part of the ESA APPRISE Oncology Program Aranesp Medication Guides are available:**
  - In each HCP Program Starter Kit provided to HCPs and hospital designees.
  - As printed copies available upon request through the ESA APPRISE Oncology Program Call Center at 1-866-284-8089

The Aranesp Medication Guide is part of the REMS and is appended.

## **B. Communication Plan**

### **Within 45 days of initial approval of the REMS Amgen will begin ongoing Healthcare Professional Communication:**

- Amgen will communicate via letter to the leadership of the relevant Nephrology professional societies, the largest dialysis organizations and nephrology group purchasing organizations. The communication will include both the Medication Guide distribution requirements and copies of the U.S. Prescribing Information, Medication Guides, and Patient Instructions for Use for Aranesp.
- Amgen will introduce the ESA APPRISE Oncology Program by mailing or emailing a Dear Healthcare Provider (DHCP) Letter to oncologists, hematologists, and other HCPs, that may potentially purchase or prescribe<sup>1</sup> Aranesp for patients with cancer and a Director of Pharmacy/Administrator letter to hospitals. The ESA APPRISE Oncology Program DHCP Letters will introduce the program, provide the rationale, program objectives, training and enrollment requirements and provide the consequences of non-enrollment. The DHCP Letters will also instruct hospitals and HCPs who prescribe, or prescribe and dispense<sup>2</sup>, Aranesp for patients with cancer how to receive training and subsequently enroll in the ESA APPRISE Oncology Program by either:
  - accessing the ESA APPRISE Oncology Program Website
  - contacting their local field-based personnel
- Amgen will communicate via letter with oncology related professional societies about the ESA APPRISE Oncology Program and provide enrollment opportunities at oncology related scientific meetings.

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<sup>1</sup> For the purposes of this REMS, the terms prescribe or prescription include medication orders in the clinic or hospital settings.

<sup>2</sup> For purposes of this REMS, dispense in a private practice setting includes dispensing for administration in a prescriber's office or under the supervision of a prescriber, such as in an infusion center.

- Amgen will also conduct targeted outreach about the ESA APPRISE Oncology Program to non-enrolled healthcare providers who prescribe, or prescribe and dispense, Aranesp for patients with cancer and non-enrolled hospitals.

**ESA APPRISE Oncology Program Website:** The website will instruct HCPs to direct any questions to their local field-based personnel or to the ESA APPRISE Oncology Program Call Center at 1-866-284-8089. The ESA APPRISE Oncology Program Call Center provides the following services:

- assistance with program training and enrollment
- supports access to program materials

The following materials are part of the REMS and are appended:

- Nephrology Professional Society Letter
- Dear Healthcare Provider (DHCP) Letter to HCPs who may purchase or prescribe ESAs for patients with cancer
- Dear Healthcare Provider (DHCP) Letter to hospital Directors of Pharmacy/Administrators
- Oncology related Professional Society Letter
- ESA APPRISE Oncology Program website
- ESA REMS Flashcard

### C. Elements to Assure Safe Use

#### 1. Healthcare providers who both prescribe and dispense Aranesp for patients with cancer in private practice settings will be specially certified, under 505-1(f)(3)(A) and (B), as follows:

- a. Amgen will ensure that physicians and other appropriately licensed healthcare providers who both prescribe and dispense Aranesp for patients with cancer in private practice settings are certified.
- b. Amgen will ensure that to become certified, each HCP completes the ESA APPRISE Oncology Program Training and enrolls into the ESA APPRISE Oncology Program by submitting a completed ESA APPRISE Oncology Program Enrollment Form and attesting to the following:
  - i. I have reviewed the current prescribing information for Aranesp.
  - ii. I understand that ESAs shortened overall survival and/or increased 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.
  - iii. I understand that in order to decrease these risks, the lowest dose of ESAs should be used to avoid red blood cell transfusion.
  - iv. I understand that Aranesp is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on

- studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, non-myeloid malignancies.
- v. I understand that ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
  - vi. I understand that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
  - vii. I understand that ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.
  - viii. I understand that ESAs should be discontinued following the completion of a chemotherapy course of treatment.
- c. Amgen will ensure that as part of the enrollment in the ESA APPRISE Oncology Program, healthcare providers attest that they have reviewed the ESA APPRISE Oncology Program requirements and agree to the following:
- i. I will discuss each patient's questions or concerns about Aranesp.
  - ii. I will provide an Aranesp Medication Guide in accordance with 21 CFR Part 208 to each oncology patient. In addition, I will provide an Aranesp Medication Guide to each oncology patient at the initiation of each new course of ESA therapy. After initiation of treatment, and for as long as treatment continues, I will provide an Aranesp Medication Guide to each oncology patient at least once a month during regular office visits.
  - iii. I will review the contents of the Medication Guide with the patient, counsel each patient on the risks (increased mortality, serious cardiovascular and thromboembolic events, and increased tumor progression or recurrence) and benefits of Aranesp I am prescribing to my patient before each new course of ESA therapy. I will document that the discussion with each patient has occurred by signing the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgement form and obtaining the patient's signature. By signing the patient section of the form, the patient acknowledges the following:
    - I acknowledge that prior to receiving my first dose of Aranesp therapy:
      - I have read and understand the Medication Guide for Aranesp that my healthcare professional has given to me.
      - I have had all my questions or concerns about Aranesp or my treatment answered by my healthcare professional.
      - I am aware that using Aranesp may make my tumor grow faster or I may get serious heart problems such as heart attack, stroke, heart failure, or blood clots, and I may die sooner.

By signing the HCP section of the form, the certified healthcare provider acknowledges the following:

- I acknowledge that prior to prescribing my patient's first dose of Aranesp therapy:
  - I provided my oncology patient with an Aranesp Medication Guide and instructed the patient to read it carefully before signing this form.
  - I counseled my patient on the risks and benefits of Aranesp, using the Medication Guide as the review tool in counseling the patient.
  - I discussed all concerns and answered all questions my patient had about Aranesp or his/her treatment to the best of my ability.
  - The patient signed the Acknowledgment Form in my presence.
- iv. I will send a signed copy of the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgement form back to the ESA APPRISE Oncology Program Call Center.
- v. I agree that the Aranesp obtained for use in my patients with cancer will not be prescribed and dispensed by an uncertified HCP.
- vi. I will ensure that Aranesp that I prescribe will be dispensed under my supervision.
- vii. I will comply with any program monitoring and auditing required to assess the effectiveness of the ESA APPRISE Oncology Program.
- d. Upon enrollment, the healthcare provider will be given a unique ESA APPRISE Oncology Program enrollment number, which will be used to confirm enrollment in the Program.
- e. Amgen will ensure that healthcare providers retrain and re-enroll into the ESA APPRISE Oncology Program every 3 years, and re-enrollment will be evaluated by a comprehensive auditing mechanism every 3 years. All healthcare providers certified in the ESA APPRISE Oncology Program will be required to retrain and re-enroll during a 1-year re-enrollment phase beginning at the 3-year anniversary of the implementation of the ESA APPRISE Oncology Program. Upon completion of retraining and re-enrollment, the healthcare provider will maintain the same ESA APPRISE Oncology Program enrollment number. Failure to re-enroll will result in suspension of access to Aranesp.
- f. Amgen will maintain a secure and accurate database of certified healthcare providers in the ESA APPRISE Oncology Program.
- g. The following materials are part of the REMS and are appended:
  - ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers

- ESA APPRISE Oncology Program Training Module for Healthcare Providers
- ESA APPRISE Oncology Program Healthcare Provider Flashcard
- Aranesp Medication Guides
- The ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgement Form
- HCP Program Starter Kit

**2. Healthcare providers who prescribe Aranesp for patients with cancer in hospitals will be specially certified, under 505-1(f)(3)(A), as follows:**

- a. Amgen will ensure that physicians and other appropriately licensed healthcare professionals who prescribe Aranesp for patients with cancer in hospitals are specially certified.
- b. Amgen will ensure that to become certified, each healthcare provider completes the ESA APPRISE Oncology Program Training, enrolls in the ESA APPRISE Oncology Program by submitting a completed ESA APPRISE Oncology Program Enrollment Form to the ESA APPRISE Oncology Program Call Center, and attests to the following:
  - i. I have reviewed the current prescribing information for Aranesp.
  - ii. I understand that ESAs shortened overall survival and/or increased 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.
  - iii. I understand that in order to decrease these risks, the lowest dose of ESAs should be used to avoid red blood cell transfusion.
  - iv. I understand that ESAs are indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for red blood cell transfusions in patients with metastatic, non-myeloid malignancies, receiving chemotherapy.
  - v. I understand that ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
  - vi. I understand that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
  - vii. I understand that ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

- viii. I understand that ESAs should be discontinued following the completion of a chemotherapy course of treatment.
- c. Amgen will ensure that as part of the enrollment in the ESA APPRISE Oncology Program, healthcare providers attest that they have reviewed the ESA APPRISE Oncology Program requirements and agree to the following:
- i. I will discuss each patient's questions or concerns about Aranesp.
  - ii. I will provide an Aranesp Medication Guide to each oncology patient at the initiation of each new course of ESA therapy. After initiation of treatment, and for as long as treatment continues, I will provide an Aranesp Medication Guide to each oncology patient at least once a month during regular office visits.
  - iii. I will review the contents of the Medication Guide with the patient, counsel each patient on the risks (increased mortality, serious cardiovascular and thromboembolic events, and increased tumor progression or recurrence) and benefits of Aranesp before each new course of Aranesp therapy. I will document that the discussion with each patient has occurred by signing the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgement form and obtaining the patient's signature. By signing the patient section of the form, the patient acknowledges the following:
    - I acknowledge that prior to receiving my first dose of Aranesp therapy:
      - I have read and understand the Medication Guide for Aranesp that my healthcare professional has given to me.
      - I have had all my questions or concerns about Aranesp or my treatment answered by my healthcare professional.
      - I am aware that using Aranesp may make my tumor grow faster or I may get serious heart problems such as heart attack, stroke, heart failure, or blood clots, and I may die sooner.

By signing the HCP section of the form, the certified healthcare provider acknowledges the following:

- I acknowledge that prior to prescribing my patient's first dose of Aranesp therapy:
  - I provided my oncology patient with an Aranesp Medication Guide and instructed the patient to read it carefully before signing this form.
  - I counseled my patient on the risks and benefits of Aranesp using the Medication Guide as the review tool in counseling the patient.

- I discussed all concerns and answered all questions my patient had about Aranesp or his/her treatment to the best of my ability.
    - The patient signed the Acknowledgment Form in my presence.
  - iv. I will comply with any program monitoring and auditing required to assess the effectiveness of the ESA APPRISE Oncology Program.
  - v. I will provide the completed ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgement form to the hospital designee responsible for maintaining and storing the forms.
- d. Upon enrollment, the healthcare provider will be given a unique ESA APPRISE Oncology Program enrollment number, which will be used to confirm enrollment in the Program.
- e. Amgen will ensure that healthcare providers retrain and re-enroll into the ESA APPRISE Oncology Program every 3 years, and re-enrollment will be evaluated by a comprehensive auditing mechanism every 3 years. All healthcare providers certified in the ESA APPRISE Oncology Program will be required to retrain and re-enroll during a 1-year re-enrollment phase beginning at the 3-year anniversary of the implementation of the ESA APPRISE Oncology Program. Upon completion of retraining and re-enrollment, the healthcare provider will maintain the same ESA APPRISE Oncology Program enrollment number. Failure to re-enroll will result in suspension of access to Aranesp.
- f. Amgen will maintain a secure and accurate database of certified healthcare providers in the ESA APPRISE Oncology Program.
- g. The following materials are part of the REMS and are appended:
  - ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers
  - ESA APPRISE Oncology Program Training Module for Healthcare Providers
  - Aranesp Medication Guides
  - The ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgement Form
  - HCP Program Starter Kit

**3. Hospitals that dispense Aranesp for patients with cancer will be specially certified under 505-1(f)(3)(B), as follows:**

- a. Amgen will ensure that hospitals that dispense Aranesp are certified through the hospital *site level enrollment* in the ESA APPRISE Oncology Program. To obtain *site level enrollment* as a hospital, the hospital designee (e.g., pharmacy director, Head of Hematology/Oncology, or other appointed designee) must complete and



sign the ESA APPRISE Oncology Program Enrollment Form for Hospitals and attest to the following:

- i. I have been designated by hospital management to assume the authority and responsibility to internally coordinate and oversee the ESA APPRISE Oncology Program requirements in my hospital. By completing enrollment, I attest to the following on behalf of my hospital:
  1. I have completed the ESA APPRISE Oncology Program Training Module.
  2. I understand that if healthcare providers in my hospital prescribe Aranesp to patients with cancer, failure of the staff to comply with enrollment requirements will lead to suspension of access to Aranesp for my hospital.
  3. I will inform all Aranesp prescribers at my hospital of the ESA APPRISE Oncology Program training and oncology prescriber certification requirements.
  4. I will establish or oversee the establishment of a system, order sets, protocols, or other measures designed to ensure that, in my hospital:
    - Aranesp is only dispensed to patients with cancer after verifying:
      - that the healthcare provider who prescribed Aranesp for patients with cancer has enrolled in the ESA APPRISE Oncology Program; and
      - that the discussion between the patient and ESA APPRISE Oncology Program-enrolled prescriber on the risks of Aranesp therapy is documented by patient and prescriber signatures on the ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgement Form prior to initiation of each new course of Aranesp therapy.
    - If a HCP that prescribes Aranesp is not enrolled in the ESA APPRISE Oncology Program, the prescriber will be notified that he/she is not able to prescribe Aranesp for patients with cancer.
  5. I am authorized to oversee compliance with program monitoring and auditing to assess the effectiveness of the ESA APPRISE Oncology Program.
  6. I will maintain evidence of compliance with the ESA APPRISE Oncology Program for monitoring and auditing purposes, as follows:
    - a list of each healthcare provider in my hospital who prescribes Aranesp for cancer patients

- documentation (i.e., unique enrollment ID number) that each healthcare provider in my hospital who prescribes Aranesp for patients with cancer is enrolled in the ESA APPRISE Oncology Program
  - documentation of the risk:benefit discussion between certified prescriber and patient by archival storage of the ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgment Form for each cancer patient for whom an Aranesp prescription was filled
- b. Upon enrollment, the hospital will be given a unique ESA APPRISE Oncology Program enrollment number that will be used to confirm enrollment in the Program.
- c. Amgen will ensure hospitals retrain and re-enroll into the ESA APPRISE Oncology Program every 3 years, and re-enrollment will be evaluated by a comprehensive auditing mechanism every 3 years. All hospitals already certified in the ESA APPRISE Oncology Program will be required to retrain and re-enroll during a 1-year re-enrollment phase beginning at the 3-year anniversary of the implementation of the ESA APPRISE Oncology Program. Failure to re-enroll will result in suspension of access to Aranesp for that hospital.
- d. Upon completion of retraining and re-enrollment, the hospital will maintain the same ESA APPRISE Oncology Program enrollment number.
- e. Amgen will ensure that the ESA APPRISE Oncology Program Call Center maintains a secure and accurate database of certified hospitals in the ESA APPRISE Oncology Program.
- f. The following materials are part of the REMS and are appended:
- ESA APPRISE Oncology Program Enrollment Form for hospitals
  - ESA APPRISE Oncology Program Training Module for Hospital Designees
  - ESA APPRISE Oncology Program Hospital Process Overview Flashcard

**4. Aranesp will be dispensed to patients with cancer with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D).**

Amgen will ensure that certified hospitals and certified HCPs agree to only dispense Aranesp to patients with cancer once the risk:benefit discussion has occurred and the patient has signed a statement with their certified HCP (the ESA APPRISE Oncology Program Patient and Healthcare Professional [HCP] Acknowledgment Form) prior to the initiation of a new course of ESA therapy.

The following materials are part of the REMS and are appended:

- The ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form

## D. Implementation System

The Implementation System includes the following:

1. Amgen will monitor compliance with documentation of the risk:benefit discussion and completion of the ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form and will work to improve implementation of these elements if non-compliance is identified.
  - a. The ESA APPRISE Oncology Program Center will conduct monitoring of all private practice-based clinics to determine compliance rates (i.e., the number of patient- and healthcare provider-signed Acknowledgment Forms returned to the ESA APPRISE Oncology Program Call Center compared to the number of patients initiating a new course of ESA therapy based on the amount of ESAs purchased) with section II.C.1 of this REMS and identify those HCPs in clinics with the poorest compliance rates. The ESA APPRISE Oncology Program Call Center will identify and audit at least 10% of the least compliant private-practice clinics with certified HCPs who prescribe ESAs to patients with cancer in the U.S. The private practice-based clinics will be audited by the ESA APPRISE Oncology Program Call Center to demonstrate evidence of compliance with the Program including:
    - i. That the number of ESA prescribers who prescribe ESAs in the Private Practice-based clinic is not greater than the number of HCPs in the private-practice based setting that are certified in the ESA APPRISE Oncology Program (by unique ESA APPRISE Oncology Program enrollment number)
    - ii. That the number of patient- and healthcare provider-signed Acknowledgment Forms returned to the ESA APPRISE Oncology Program Call Center is not less than the number of patients initiating a new course of ESA therapy. For the audits to be effective, private practiced based clinics will implement a means to determine the total number of individual patients that received Aranesp based on orders and prescriptions written.
    - iii. Each audit will be conducted according to a time schedule that allows these data to be provided with each REMS assessment.
  - b. For hospitals, the ESA APPRISE Oncology Program Call Center will identify a random sample of certified hospitals enrolled in accordance with section II.C.3 of this REMS (at least 25). These hospitals will be audited by the ESA APPRISE Oncology Program Call Center to demonstrate evidence of compliance with the Program including:
    - i. That the documentation maintained by hospitals demonstrates that each healthcare provider in the hospitals who prescribe ESAs for patients with cancer is certified in the ESA APPRISE Oncology Program (by unique ESA APPRISE Oncology Program enrollment number)

- ii. That the number of patient- and healthcare provider-signed Acknowledgment Forms retained at the hospital is not less than the number of patients initiating a new course of ESA therapy. For the audits to be effective, hospitals will implement a means to determine the total number of individual patients that received Aranesp based on orders and prescriptions written.
  - iii. For sites that are non-compliant, the ESA APPRISE Oncology Program Call Center will evaluate the reasons for non-compliance.
  - iv. The audits will be conducted according to a time schedule that allows these data to be provided with each REMS assessment.
2. Following an enrollment period post approval (not to exceed 12 months), Amgen will ensure that distributors will not ship an ESA to a hospital or healthcare provider at a private practice-based clinic without confirmation from the ESA APPRISE Oncology Program Call Center that the hospital is certified under Section II.C.3 or the healthcare provider is certified under Section II.C.1 or that certification is not applicable (i.e., that the hospital does not dispense an ESA for patients with cancer or that the healthcare provider does not prescribe and dispense an ESA for patients with cancer in a private practice setting).
3. Amgen will monitor HCP enrollment under II.C.1. on an ongoing basis to evaluate compliance with the ESA APPRISE Oncology Program enrollment requirements and will work to improve implementation of this element.
4. Amgen will monitor hospital enrollment under II.C.3 on an ongoing basis to evaluate compliance with the ESA APPRISE Oncology Program enrollment requirements and will work to improve implementation of this element.

Based on monitoring and evaluation of these elements to assure safe use, Amgen will take reasonable steps to improve implementation of these elements.

#### **E. Timetable for Submission of Assessments of the REMS**

Amgen will submit REMS Assessments at 8 months, 1 year, 18 months, and annually thereafter following the 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. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.