

Initial REMS Approval: 02/2010

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BL 103951 ARANESP® (DARBEPOETIN ALFA)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

To support informed discussions between patients with cancer and their healthcare providers by:

- educating healthcare providers about the risks and safe use conditions of Aranesp for patients with cancer.
- informing patients about the risk of shortened overall survival and/or increased risk of tumor progression or recurrence when Aranesp is used to treat anemia due to concomitant myelosuppressive chemotherapy.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers (HCPs) who both prescribe¹ and dispense² Aranesp for patients with cancer in private practice settings and healthcare providers who prescribe Aranesp for patients with cancer in hospitals are specially certified.

- a. Amgen will ensure that HCPs who both prescribe and dispense Aranesp for patients with cancer in private practice settings and HCPs who prescribe Aranesp for patients with cancer in hospitals are certified.

To become specially certified, each HCP must enroll in the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs {erythropoiesis stimulating agents}) Oncology Program by doing the following:

- i. Review the prescribing information.

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

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

- ii. Complete the ESA APPRISE Oncology Program Training Module for Healthcare Providers.
- iii. Complete and sign the ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers and submit it to the ESA APPRISE Oncology Program Call Center.
- iv. Agree to counsel each patient on the risks of ESAs by reviewing and signing the ESA APPRISE Oncology Program Patient and Healthcare Provider Acknowledgment Form (Acknowledgment Form) (or modified version consistent with the allowable changes) and to provide a copy of the signed Acknowledgment Form to the patient.
 - 1) HCPs in a private clinic practice setting agree to maintain a completed Acknowledgment Form for auditing purposes in a manner that does not require the disclosure of the patient's medical record, and to store the Acknowledgment Forms on-site and/or archive them in a retrievable manner.
 - 2) HCPs in a hospital setting agree to provide the completed Acknowledgment Forms to the Hospital Designee responsible for maintaining and storing the forms on-site and/or archiving them in a retrievable manner.

b. Amgen will:

- i. Send a DHCP Letter to non-certified HCPs who may prescribe, or prescribe and dispense, Aranesp for patients with cancer instructing them how to become certified in the ESA APPRISE Oncology Program.
- ii. Provide each certified HCP a unique ESA APPRISE Oncology Program enrollment identification (ID) number, which will be used to confirm certification in the Program.
- iii. Maintain a secure and accurate database of HCPs certified in the ESA APPRISE Oncology Program.
- iv. Ensure that, as part of the enrollment process, HCPs receive the following materials that are part of the ESA APPRISE Oncology Program:
 - 1) Dear Healthcare Provider (DHCP) Letter to Newly Identified HCPs who may Prescribe, or Prescribe and Dispense, ESAs for Patients with Cancer
 - 2) ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers
 - 3) ESA APPRISE Oncology Program Training Module for Healthcare Providers
 - 4) Steps for Healthcare Providers Who Prescribe, or Prescribe and Dispense, ESAs for Patients With Cancer

- 5) ESA APPRISE Oncology Program Patient and Healthcare Provider Acknowledgment Form
- 6) Guidelines for Acknowledgment Form Integration Within Healthcare Systems and Clinics
- v. Inform certified HCPs following important modifications to the Aranesp REMS or to the ESA APPRISE Oncology Program
- vi. Ensure that ESA APPRISE Oncology Program materials are available on the Program website or can be obtained by contacting the ESA APPRISE Oncology Program Call Center at 1-866-284-8089.

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

- Dear Healthcare Provider (DHCP) Letter to Newly Identified HCPs who may Prescribe, or Prescribe and Dispense, ESAs for Patients with Cancer
- ESA APPRISE Oncology Program Enrollment Form for Healthcare Providers
- ESA APPRISE Oncology Program Training Module for Healthcare Providers
- Steps for Healthcare Providers Who Prescribe, or Prescribe and Dispense, ESAs for Patients With Cancer
- ESA APPRISE Oncology Program Patient and Healthcare Provider Acknowledgment Form
- ESA APPRISE Oncology Program Website

2. Hospitals that dispense Aranesp for patients with cancer are specially certified.

- a. Amgen will ensure that hospitals that dispense Aranesp are certified in the ESA APPRISE Oncology Program.

To become specially certified, a Hospital Designee (eg, Pharmacy Director, Head of Hematology/Oncology, or other appointed designee) must enroll into the ESA APPRISE Oncology Program by doing the following:

- i. Complete the ESA APPRISE Oncology Program Training Module for Hospital Designees.
- ii. Agree to assume the authority and responsibility to internally coordinate and oversee the ESA APPRISE Oncology Program requirements in hospital(s) for which they are responsible.
- iii. Agree to establish or oversee the establishment of a system, order sets, protocols, or other measures designed to ensure that the hospital is in compliance with the ESA APPRISE Oncology Program, such that:
 - 1) Aranesp is only dispensed to patients with cancer after verifying:

- a) that the healthcare provider who prescribed Aranesp for patients with cancer is certified in the ESA APPRISE Oncology Program; and
 - b) the discussion between the patient and ESA APPRISE Oncology Program-certified provider on the risks of Aranesp therapy is documented by patient and provider signatures on the Acknowledgment Form (or modified version consistent with the allowable changes) prior to initiation of each new course of Aranesp therapy.
- 2) If an HCP that prescribes Aranesp is not certified in the ESA APPRISE Oncology Program, the provider will be notified that they are not able to prescribe Aranesp for patients with cancer.
- iv. Oversee compliance with program auditing to assess the effectiveness of the ESA APPRISE Oncology Program.
 - v. Maintain evidence of compliance with the ESA APPRISE Oncology Program for auditing purposes, as follows:
 - 1) documentation (ie, unique enrollment ID number) that each HCP in the hospital who prescribes Aranesp for patients with cancer is certified in the ESA APPRISE Oncology Program
 - 2) documentation of the risk:benefit discussion between certified provider and patient on the Acknowledgment Form (or modified version consistent with the allowable changes) for each patient with cancer for whom an Aranesp prescription was filled; the Acknowledgment Forms are to be stored on-site and/or archived in a retrievable manner.
 - vi. Complete and sign the ESA APPRISE Oncology Program Enrollment Form for Hospitals and submit it to the ESA APPRISE Oncology Program Call Center.
- b. Amgen will:
 - i. Send a Dear Director of Pharmacy/Administrator Letter to non-certified hospitals that dispense Aranesp for patients with cancer, instructing them how to become certified in the ESA APPRISE Oncology Program.
 - ii. Provide each hospital with a unique ESA APPRISE Oncology Program enrollment ID number that will be used to confirm certification in the Program.
 - iii. Ensure that the ESA APPRISE Oncology Program Call Center maintains a secure and accurate database of certified hospitals in the ESA APPRISE Oncology Program.

- iv. Ensure that, as part of the enrollment process, the Hospital Designee receives the following materials that are part of the ESA APPRISE Oncology Program:
 - 1) Dear Healthcare Provider (DHCP) Letter to Directors of Pharmacy/Administrators of Newly Identified Hospitals That Dispense ESAs to Patients With Cancer
 - 2) ESA APPRISE Oncology Program Enrollment Form for Hospitals
 - 3) ESA APPRISE Oncology Program Training Module for Hospital Designees
 - 4) Steps for Hospitals and Hospital/Institution-affiliated Outpatient Facilities That Dispense ESAs to Patients With Cancer
 - 5) Steps for Healthcare Providers Who Prescribe, or Prescribe and Dispense, ESAs for Patients With Cancer
 - 6) ESA APPRISE Oncology Program Patient and Healthcare Provider Acknowledgment Form
 - 7) Guidelines for Acknowledgment Form Integration Within Healthcare Systems and Clinics
- v. Inform certified Hospital Designees following important modifications to the Aranesp REMS or to the ESA APPRISE Oncology Program.
- vi. Ensure that ESA APPRISE Oncology Program materials are available on the Program website or can be obtained by contacting the ESA APPRISE Oncology Program Call Center at 1-866-284-8089.

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

- Dear Healthcare Provider (DHCP) Letter to Directors of Pharmacy/Administrators of Newly Identified Hospitals That Dispense ESAs to Patients With Cancer
- ESA APPRISE Oncology Program Enrollment Form for Hospitals
- ESA APPRISE Oncology Program Training Module for Hospital Designees
- Steps for Hospitals and Hospital/Institution-affiliated Outpatient Facilities That Dispense ESAs to Patients With Cancer

3. Aranesp will be dispensed to patients with cancer with evidence or other documentation of safe-use conditions.

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 patients and their certified HCPs have signed the Acknowledgment Form (or modified version consistent with the allowable changes) prior to the initiation of each new course of ESA therapy.

B. Implementation System

The Implementation System includes the following:

1. Amgen will monitor compliance with completion of the Acknowledgment Form (or modified version consistent with the allowable changes) and will work to improve implementation if non-compliance is identified.
 - a. Amgen will allow certain changes to the Acknowledgment Form to ensure that the form can be adapted by hospitals and private practices to be compatible with their existing systems. The allowable formatting-related changes are:
 - i. Removal of title instruction and footnoted text
 - ii. Addition of patient identifier and/or clinic/hospital identifiers (eg, name and/or logo, barcodes)
 - iii. Changes to make the form compatible with existing systems, including electronic- and paper-based systems

The content in the Patient and HCP sections of the Acknowledgment Form cannot be changed. No content can be added or removed from these sections.

The Guidelines for Acknowledgment Form Integration Within Healthcare Systems and Clinics is part of the REMS and is appended.

- b. The ESA APPRISE Oncology Program will audit selected private practice-based clinics. For each audit, a sample of at least 100 clinics that have purchased ESAs during the audit period that were not included in the prior audit will be selected. Each audit will be conducted according to a time schedule that allows these data to be provided with each REMS assessment. HCPs in private practice-based clinics will be audited by the ESA APPRISE Oncology Program to demonstrate evidence of compliance with the Program as follows:
 - i. That the number of HCPs who prescribe ESAs for patients with cancer 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 ID number).
 - ii. That the number of patient- and HCP-signed Acknowledgment Forms retained at the clinic is not less than the number of patients with cancer initiating a new course of ESA therapy.
- c. For hospitals, the ESA APPRISE Oncology Program will identify at least 25 hospitals with ESA use in patients with cancer during the audit period. The audits will be conducted according to a time schedule that allows these data to be provided with each REMS assessment. These hospitals will be audited by the ESA APPRISE Oncology Program to demonstrate evidence of compliance with the Program as follows:

- i. That the documentation maintained by hospitals demonstrates that each HCP 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 ID number).
 - ii. That the number of patient- and HCP-signed Acknowledgment Forms retained at the hospital is not less than the number of patients with cancer 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.
2. For sites that are non-compliant, Amgen will request that the non-compliant clinic or hospital develop, submit, and implement a plan to correct findings. The site will automatically be included in a for-cause audit for the subsequent audit cycle. If continued non-compliance is identified, the HCP or hospital will have their access to ESAs suspended. Removal from the Suspended Access List will require correction of non-compliance with the REMS requirements.
3. Amgen will instruct distributors not to ship an ESA to a hospital or HCP at a private practice-based clinic without confirmation from the ESA APPRISE Oncology Program Call Center that the hospital or the HCP is certified or that certification is not applicable (ie, the hospital does not dispense an ESA for patients with cancer or the HCP does not prescribe, or prescribe and dispense, an ESA for patients with cancer in a private practice-based clinic).
4. Amgen will monitor HCP and hospital certification on an ongoing basis to evaluate compliance with the ESA APPRISE Oncology Program certification requirements and will work to improve implementation of this element.
5. If there are important modifications to the Aranesp REMS and to the ESA APPRISE Oncology Program, Amgen will update all affected materials and notify certified HCPs and hospitals, as applicable.

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

C. Timetable for Submission of Assessments of the REMS

Amgen will submit REMS Assessments at 8 months, 1 year, 18 months, 24 months, and annually thereafter following the initial approval (02/2010) 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.