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## Drugs

### FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp

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#### Safety Announcement

The FDA is requiring all drugs called Erythropoiesis-Stimulating Agents (ESAs) to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy (REMS), to ensure the safe use of these drugs. The ESAs that are part of the REMS are marketed under the names Epogen, Procrit, and Aranesp. FDA required Amgen, the manufacturer of these products, to develop a risk management program because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions.

ESAs work by stimulating the bone marrow to produce red blood cells. ESAs are approved for the treatment of anemia (low red blood cells) resulting from chronic kidney failure, chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), and also to reduce the number of blood transfusions during and after certain major surgeries.

As part of the REMS, a *Medication Guide* explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs. In addition to the Medication Guide, Amgen was required to develop the ESA APPRIS (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program for healthcare professionals who prescribe ESAs to patients with cancer.

Under the ESA APPRIS Oncology program, Amgen will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer. Amgen is also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program.

The goals of the REMS for the ESAs are:

- To support informed decisions between patients and their healthcare professionals who are considering treatment with an ESA by educating them on the risks of ESAs.
- To mitigate the risk of decreased survival and/or poorer tumor outcomes in patients with cancer by implementing the part of the REMS called the ESA APPRIS Oncology Program.

#### **Additional Information for Patients:**

##### **Patients with cancer**

Patients using ESAs should:

- Understand the risks associated with use of ESAs. These risks include:
  - ESAs may cause tumors to grow faster.
  - ESAs may cause some patients to die sooner.
  - ESAs may cause some patients to develop blood clots, and serious heart problems such as a heart attack, heart failure or stroke.

- Be aware that their healthcare professional has received special training about the use of ESAs in patients with cancer.
- Read the **Medication Guide** to understand the benefits and risks of using an ESA.
- Talk with their healthcare professional about any questions they may have about using ESAs.
- Be aware that they will be asked to sign an acknowledgment form that says they have talked with their healthcare professional about the risks of ESAs. This form must be signed before patients begin a course of treatment with an ESA.

**Patients with chronic kidney failure** (includes patients on dialysis and those not on dialysis)

**Patients using ESAs should:**

- Know that the use of ESAs can increase the risk for stroke, heart attack, heart failure, blood clots, and death.
- Read the **Medication Guide** to understand the benefits and risks of using an ESA.
- Get blood tests while using ESAs. The test results may help guide the course of therapy and lower the risks of using these drugs. Patients' healthcare professionals should make them aware of how often to have blood tests.
- Talk with their healthcare professional about any questions they have about the risks and benefits of using ESAs.

### Additional Information for Healthcare Professionals and Hospitals: ESA use in cancer

#### Healthcare Professionals

The ESA APPRISE Oncology program requires that all healthcare professionals who prescribe ESAs for patients with cancer do the following:

- Complete a training module that covers the use of ESAs. Completion of the training module is required for enrollment in the ESA APPRISE Oncology program.
- Sign the patient/healthcare professional acknowledgement form prior to the patient receiving an ESA. The acknowledgement form attests that the healthcare professional and patient have discussed the risks of using an ESA.
- Re-enroll in the ESA APPRISE Oncology program every three years.

Healthcare professionals not enrolled in the ESA APPRISE Oncology program will not be able to prescribe ESA for use in patients with cancer.

As part of the enrollment in the ESA APPRISE Oncology program, healthcare professionals must attest to their understanding of the following:

- 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 cancer.
- To decrease the risks of ESAs, the lowest dose needed should be used to avoid red blood cell transfusion.
- ESAs should be discontinued following completion of a chemotherapy course of treatment.
- Aranesp<sup>®</sup> 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.
- Epogen<sup>®</sup>/Procrit<sup>®</sup> 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 receiving chemotherapy for a minimum of 2 months.
- ESAs are not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

**Hospitals**

Hospitals must do the following:

- Be enrolled in the ESA APPRISE Oncology program in order to dispense ESAs to patients with cancer, even if the prescribing healthcare professional is certified under the program.
- Have a system in place that ensures that all healthcare providers who prescribe ESAs in the hospital are enrolled and comply with the ESA APPRISE Oncology program.

**Additional Information for Healthcare Professionals: non-cancer use of ESAs**

- Healthcare professionals who prescribe ESAs for anemia not caused by cancer chemotherapy are required to provide a copy of the *Medication Guide* to each patient or their representative when an ESA is dispensed.
- Healthcare professionals who use ESAs only for non-cancer uses are not required to enroll in the ESA APPRISE Oncology program.

**Evaluation and Monitoring of the APPRISE Oncology Program**

Amgen will be responsible for ensuring compliance with the program:

- Amgen will conduct real-time monitoring of prescribing and purchases in private-practice settings and clinic audits.
- Hospitals in the program will be audited to ensure compliance with the ESA APPRISE Oncology Program.
- Failure to comply will result in a suspension of access to ESAs.

**Table of Key Safety Studies**

Study/Tumor/(n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1, Q3)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
<b>Chemotherapy</b>				
<b>Cancer Study 1</b>				
Metastatic breast cancer (n=939)	12-14g/dL	12.9 g/dL 12.2, 13.3 g/dL	12 month overall survival	Decreased 12-month survival
<b>Cancer Study 2</b>				
Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
<b>Cancer Study 3</b>				
Early breast cancer (n=733)	12.5-13 g/dL	13.1 g/dL 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3 yr. relapse-free and overall survival
<b>Cancer Study 4</b>				
Cervical Cancer (n=114)	12-14 g/dL	12.7 g/dL 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3 yr. progression-free and overall survival and locoregional control
<b>Radiotherapy Alone</b>				
<b>Cancer Study 5</b>				
Head and neck cancer (n=351)	≥15 g/dL (M) ≥14 g/dL (F)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
<b>Cancer Study 6</b>				
	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control

Hand and neck cancer

(n=522)

**No Chemotherapy or Radiotherapy**

**Cancer Study 7**

Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of Life	Decreased overall survival
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**Cancer Study 8**

Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival
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**Related Information**

- [Information on Erythropoiesis-Stimulating Agents \(ESA\) Epoetin alfa \(marketed as Procrit, Epogen\) Darbepoetin alfa \(marketed as Aranesp\)](#) <sup>1</sup>
- [Aranesp REMS \(PDF - 11146KB\)](#) <sup>2</sup>
- [Aranesp Medication Guide \(PDF - 59KB\)](#) <sup>3</sup>
- [Letter Regarding Aranesp Medication Guide \(PDF - 40KB\)](#) <sup>4</sup>  
3/12/2010
- [Darbepoetin Alfa \(marketed as Aransep\) Label - 2/16/2010](#) <sup>5</sup>
- [Epogen/Procrit REMS \(PDF - 11043KB\)](#) <sup>6</sup>
- [Epogen Medication Guide \(PDF - 62KB\)](#) <sup>7</sup>
- [Procrit Medication Guide \(PDF - 57KB\)](#) <sup>8</sup>
- [Letter Regarding Epogen/Procrit Medication Guide \(PDF - 39KB\)](#) <sup>9</sup>  
3/12/2010
- [Epoetin Alfa \(marketed as Epoetin, Procrit\) Label - 2/16/2010](#) <sup>10</sup>
- [FDA Announces New Safety Plan for Agents Used to Treat Chemotherapy-Related Anemia](#) <sup>11</sup>  
2/16/2010
- [Transcript for FDA's Stakeholder Meeting on Agents Used to Treat Chemotherapy-Related Anemia \(Erythropoiesis-Stimulating Agents\) \(PDF - 44KB\)](#) <sup>12</sup>  
3/5/2010
- [FDA's Stakeholder Meeting on Agents Used to Treat Chemotherapy-Related Anemia \(Erythropoiesis-Stimulating Agents\) - mp3 \(MP3 - 4216KB\)](#) <sup>13</sup>  
3/5/2010

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• **Report a Serious Problem**

- 1-800-332-1088
- 1-800-FDA-0178 Fax
- [MedWatch Online](#) <sup>14</sup>

**Regular Mail:** Use postage-paid [FDA Form 3500](#) <sup>15</sup>

**Mail to:** MedWatch 5600 Fishers Lane

Rockville, MD 20852-9787

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