



IMPORTANT PRESCRIBING INFORMATION

SUBJECT: Updated Aranesp[®] (darbepoetin alfa) and EPOGEN[®]/PROCRIT[®] (epoetin alfa) United States Prescribing Information (USPI) for patients with chronic kidney disease (CKD)

June 24, 2011

Dear Health Care Provider:

In collaboration with the Food and Drug Administration (FDA), Amgen and Janssen Products, LP have updated the Aranesp and EPOGEN/PROCRIT product labeling to provide new dosage and administration instructions for patients with CKD based on the results from three randomized, controlled trials. In these trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. The dosing guidance is now different for patients with CKD on dialysis and not on dialysis. In addition, other sections of the USPIs, including the Boxed Warning and Warnings and Precautions, have been modified. Please see the enclosed full prescribing information for more information on the use of these products.

The USPIs have also been revised to comply with the formatting requirements of the Physician Labeling Rule. Following this conversion, sections in the USPIs have been reordered and reorganized, and other minor text revisions were made to improve overall readability.

Important changes to the Dosage and Administration (Section 2.2) of the USPIs for the treatment of patients with CKD include the following:

In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell (RBC) transfusions [*see Warnings and Precautions (5.1)*]. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events [*see Boxed Warning and Clinical Studies (14)*].

For all patients with CKD:

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin

excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of ESA by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the ESA dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue ESA if responsiveness does not improve.

For patients with CKD on dialysis:

- Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.
- *EPOGEN/PROCRIT Only:* The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously. For pediatric patients, a starting dose of 50 Units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis.
- *Aranesp Only:* The recommended starting dose is 0.45 mcg/kg intravenously or subcutaneously as a weekly injection or 0.75 mcg/kg once every 2 weeks as appropriate. The intravenous route is recommended for patients on hemodialysis.

For patients with CKD not on dialysis:

- Consider initiating ESA treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
 - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and,
 - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA, and use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.
- *EPOGEN/PROCRIT Only:* The recommended starting dose for adult patients is 50 to 100 Units/kg 3 times weekly intravenously or subcutaneously.
- *Aranesp Only:* The recommended starting dose is 0.45 mcg/kg body weight intravenously or subcutaneously given once at four week intervals as appropriate.

When treating patients who have CKD and cancer, physicians should refer to *Warnings and Precautions (5.1 and 5.3)*.

Refer patients who self-administer ESA to the Instructions for Use [*see Patient Counseling Information (17)*].

In addition, the Boxed Warning, Warnings and Precautions (Section 5.1) and Clinical Studies (Section 14.1) have been updated to advise that the use of ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions. The revised Boxed Warning of the USPIs is shown below.

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions*].**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [see *Table 2 in EPOGEN/PROCRIT and Table 3 in Aranesp, Warnings and Precautions*].**
- **Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology program to prescribe and/or dispense ESA to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance [see *Warnings and Precautions*].**
- **To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions [see *Dosage and Administration*].**
- **Use ESAs only for anemia from myelosuppressive chemotherapy [see *Indications and Usage*].**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure [see *Indications and Usage*].**
- **Discontinue following the completion of a chemotherapy course [see *Dosage and Administration*].**

Perisurgery (EPOGEN/PROCRIT only):

- **Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended [see *Dosage and Administration and Warnings and Precautions*].**

These are not the only risks associated with the use of these products. Please see the enclosed full prescribing information for more information about the risks associated with the use of these products. This information is also available at www.aranesp.com, www.epogen.com, and www.procrit.com.

Should you have any questions, require further information on product safety, or wish to report adverse patient experiences, please contact:

- For Aranesp[®] and EPOGEN[®]: Amgen's Medical Information Connection™ at 1-800-77-AMGEN
- For PROCRT[®]: Janssen Scientific Affairs, LLC Medical Information at 1-800-526-7736

Alternatively, adverse events may be reported to FDA's MedWatch reporting system:

- by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178),
- online (<https://www.accessdata.fda.gov/scripts/medwatch/>), or
- by mail using the MedWatch Form FDA 3500 postage paid form, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,



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