

## Questions and Answers on Erythropoiesis-stimulating Agents (ESAs)

Epoetin alfa (marketed as Procrit, Epogen)

Darbepoetin alfa (marketed as Aranesp)

### **What is the FDA announcing today?**

The FDA is announcing new safety information about erythropoiesis-stimulating agents (ESAs). Erythropoiesis-stimulating agents (ESAs) are man-made versions of a natural protein. The natural protein is made by the kidney and stimulates the bone marrow to produce more red blood cells. ESAs are given to reduce the number of red blood cell transfusions administered to patients with certain serious diseases/conditions who are or may become anemic. The new information from recently reported clinical studies includes the following:

- Chronic kidney failure patients had increased numbers of deaths and of non-fatal heart attacks, strokes, heart failure, and blood clots when ESAs were adjusted to maintain higher red blood cell levels (hemoglobin more than 12 g/dL).
- Head and neck cancer patients receiving radiation therapy had faster tumor growth when ESAs were adjusted to maintain hemoglobin levels higher than 12 g/dL.
- Cancer patients not receiving chemotherapy died sooner and had no fewer blood transfusions when ESAs were given according to the dosing recommendations for cancer patients receiving chemotherapy.
- Patients scheduled for orthopedic surgery who received ESAs to reduce blood transfusions during and after surgery had more blood clots than those not given an ESA

### **What are the FDA-approved uses for ESAs?**

ESAs are approved for use in anemic patients with chronic kidney failure, for anemic patients with cancer taking chemotherapy, for anemic patients with HIV taking zidovudine (AZT), and for patients with hemoglobin levels of 10-13 g/dL prior to surgical procedures expected to require blood transfusions and who are unwilling to donate blood.

ESAs are not approved to treat the symptoms of anemia, including fatigue, tiredness, low energy, poor quality of life, shortness of breath, and dizziness.

### **What products are covered by FDA's public health advisory?**

The products are darbepoetin alfa and epoetin alfa. Darbepoetin alfa was approved for marketing on September 17, 2001 and is licensed and marketed by Amgen, Inc. as Aranesp. Epoetin alfa was approved for marketing on June 1, 1989 and is also licensed by Amgen, Inc. It is marketed under the proprietary name Procrit by Ortho Biotech L.P., a subsidiary of Johnson and Johnson Pharmaceutical Research & Development LLC (J&J PRD), and marketed under the proprietary name Epogen by Amgen, Inc.

**Does this new information about safety risks apply to all of these products?**

Yes, the safety risks apply to all ESAs.

**What is FDA doing?**

To inform the general public, FDA issued a public health advisory, a press release, and scheduled a press call. FDA has approved revised product labeling for physicians and patients that describes new warnings and dosing information. FDA posted an “Information for Health Care Professionals” sheet to further inform prescribers and other health care professionals (<http://www.fda.gov/cder/drug/infopage/RHE/default.htm>).

The Agency will present this new information to the Oncologic Drugs Advisory Committee on May 10, 2007. FDA will seek advice on the need for additional labeling changes and/or additional studies to further assess safety.

FDA informed hematologists, oncologists and nephrologists via an additional e-mail communication that will be distributed through medical professional organizations; this will be posted on FDA’s Office of Oncology Drug Products website (<http://www.fda.gov/cder/Offices/OODP/default.htm>), under the “What’s New” link.

FDA will issue a letter to all IND holders investigating new uses of ESAs. This letter will describe the new data, advise discussion of this information with patients, investigators, and IRBs, and recommend re-consideration of the safety of studies in light of these new data.

FDA asked Amgen, Ortho Biotech, LP, and other ESA manufacturers to provide FDA with the results of clinical studies describing increased risks of ESAs.

FDA requested that Amgen and Ortho Biotech, LP provide an overview and update on the status of all studies investigating safety of ESAs, particularly agreed-upon post-marketing studies and studies identified at the May 2004 ODAC meeting.

**What are Amgen, Inc. and Ortho Biotech doing?**

They have revised product labeling to include the new warnings and dosing recommendations and will issue the revised labeling with a Dear Health Care Provider letter. They have voluntarily agreed to suspend broadcast (radio and television) direct-to-consumer advertising for Aranesp, Procrit, and Epogen regarding uses in cancer, with the

exception of safety information, under after the May 2007 ODAC meeting. Amgen and Ortho Biotech agreed to inform all investigators conducting company-sponsored or supported studies of these data, to revise investigational drug brochures, and to participate in the May 2007 ODAC meeting.

### **What should physicians and healthcare professionals do with this information?**

Physicians should discuss this information with patients in clinical studies and should ask patients to confirm their consent for continued participation. Institutional Review Boards should also be advised of these findings. Investigators should re-evaluate whether clinical investigations should continue in light of these new safety data.

### **What previous actions has FDA taken regarding safety concerns with ESAs?**

The product labels for all US marketed ESAs have been updated several times since the original approvals to incorporate new safety information. The FDA has closely monitored emerging safety information and requested post-marketing studies to address actual and potential safety concerns. These included requests for post-marketing studies to assess risks of blood clots and effects on cancer. FDA has requested and performed analyses of clinical studies to assess the relationship between safety, dose, and pharmacodynamic effects (e.g., rate of increase of red blood cells). FDA also sought advice of the ODAC in May 2004 regarding assessment of current information and design of studies to assess effects on tumor growth, increased death rate, and blood clots.

As new data became available, FDA approved labeling changes when the information available was determined to be sufficient to support the change.

### **Should patients consider alternative products?**

Yes, the patient and his/her physician should carefully consider the risks of ESAs and the risks of red blood cell transfusions (an alternative treatment for anemia) before making a decision to use ESAs.

### **Why isn't FDA removing ESAs from the market?**

At this time, ESAs appear to be safe and effective when used according to the recently revised product labeling, at the recommended dose and approved indication. The revised labeling reflects the current knowledge regarding risks and benefits that patients and their physicians should consider. The FDA continues to assess data as it becomes available.

### **ESAs may be used in ways that are not FDA-approved. Should those users be concerned in the wake of these studies?**

Yes, all users of ESAs should be aware of these risks. Those taking ESAs may be at increased risk of death and of serious cardiovascular complications, including stroke,

heart attack, pulmonary embolism, and deep vein thrombosis (blood clots to the heart and the blood vessels).

**What are the previously reported serious and life-threatening side effects of ESAs when used according to FDA-approved product labeling?**

Serious and life-threatening side effects common to all ESAs include:

- An increased risk of blood clots in the lungs, brain and major blood vessels.
- Pure red cell aplasia. This is a severe anemia that results when patients become allergic to erythropoietins.

Serious and life-threatening side effects in patients with chronic kidney failure

- Seizures
- Hypertensive encephalopathy (swelling of the brain caused by very high blood pressure)

**Where can I find more information about ESAs?**

Please see the ESA information web page at <http://www.fda.gov/cder/drug/infopage/RHE/default.htm>.