IMPORTANT SAFETY INFORMATION

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

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 RETACRIT™ dose sufficient to reduce the need for red blood cell (RBC) transfusions.

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.

• To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.

• Use ESAs only for anemia from myelosuppressive chemotherapy.

• ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.

• Discontinue following the completion of a chemotherapy course.

PERISURGERY:

• Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended.

CONTRAINDICATIONS

RETACRIT™ is contraindicated in patients with:

• Uncontrolled hypertension.

• Pure red cell aplasia (PRCA) that begins after treatment with RETACRIT™ or other erythropoietin protein drugs.

• Serious allergic reactions to RETACRIT™ or other epoetin alfa products.

INCREASED MORTALITY, MYOCARDIAL INFARCTION, STROKE, AND THROMBOEMBOLISM

• In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), epoetin alfa increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.

• Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin...
response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.

- In controlled clinical trials of patients with cancer, epoetin alfa increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

INCREASED MORTALITY AND/OR INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE IN PATIENTS WITH CANCER

- ESAs resulted in decreased locoregional control/progression-free survival (PFS) and/or overall survival (OS). Adverse effects on PFS and/or OS were observed in studies of patients receiving chemotherapy for breast cancer, lymphoid malignancy, and cervical cancer; in patients with advanced head and neck cancer receiving radiation therapy; and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

HYPERTENSION

- RETACRIT™ is contraindicated in patients with uncontrolled hypertension. Following initiation and titration of epoetin alfa, approximately 25% of patients on dialysis required initiation of or increases in antihypertensive therapy; hypertensiveencephalopathy and seizures have been reported in patients with CKD receiving RETACRIT™.
- Appropriately control hypertension prior to initiation of and during treatment with RETACRIT™. Reduce or withhold RETACRIT™ if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

SEIZURES

- Epoetin alfa products, including RETACRIT™, increase the risk of seizures in patients with CKD. During the first several months following initiation of RETACRIT™, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms or change in seizure frequency.

LACK OR LOSS OF HEMOGLOBIN RESPONSE TO RETACRIT™

- For lack or loss of hemoglobin response to RETACRIT™, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to RETACRIT™ therapy.

PURE RED CELL APLASIA

- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with epoetin alfa. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which RETACRIT™ is not approved).
- If severe anemia and low reticulocyte count develop during treatment with RETACRIT™, withhold RETACRIT™ and evaluate patients for neutralizing antibodies to erythropoietin. Contact Pfizer Inc. at 1-800-438-1985 to perform assays for binding and neutralizing antibodies. Permanently discontinue RETACRIT™ in
patients who develop PRCA following treatment with RETACRIT™ or other erythropoietin protein drugs. Do not switch patients to other ESAs.

SERIOUS ALLERGIC REACTIONS

- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with epoetin alfa products. Immediately and permanently discontinue RETACRIT™ and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

SEVERE CUTANEOUS REACTIONS

- Blistering and skin exfoliation reactions, including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including epoetin alfa) in the postmarketing setting. Discontinue RETACRIT™ therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

RISK IN PATIENTS WITH PHENYLKETONURIA

- Phenylalanine can be harmful to patients with phenylketonuria (PKU). RETACRIT™ contains phenylalanine, a component of aspartame. Each 1 mL single-dose vial of 2,000, 3,000, 4,000, 10,000, and 40,000 Units of epoetin alfa-epbx injection contains 0.5 mg of phenylalanine. Before prescribing RETACRIT™ to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including RETACRIT™.

DIALYSIS MANAGEMENT

- Patients may require adjustments in their dialysis prescriptions after initiation of RETACRIT™. Patients receiving RETACRIT™ may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

- Adverse reactions in ≥5% of epoetin alfa-treated patients on dialysis were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion and upper respiratory tract infection.

ANEMIA DUE TO CHEMOTHERAPY IN PATIENTS WITH CANCER

- Adverse reactions in ≥5% of epoetin alfa-treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis.

SURGERY/PERISURGERY

- Adverse reactions in ≥5% of epoetin alfa-treated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension.

ANEMIA DUE TO ZIDOVUDINE IN PATIENTS WITH HIV-INFECTION

- Adverse reactions in ≥5% of epoetin alfa-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation.

INDICATIONS AND LIMITATIONS OF USE

ANEMIA DUE TO CHRONIC KIDNEY DISEASE

RETACRIT™ is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis, to decrease the need for red blood cell (RBC) transfusion.

ANEMIA DUE TO ZIDOVUDINE IN PATIENTS WITH HIV-INFECTION

RETACRIT™ is indicated for the treatment of anemia due to zidovudine administered at ≤4,200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of ≤500 mUnits/mL.
ANEMIA DUE TO CHEMOTHERAPY IN PATIENTS WITH CANCER

RETACRIT™ is indicated for the treatment of anemia in patients with nonmyeloid malignancies where

anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

REDUCTION OF ALLOGENEIC RED BLOOD CELL TRANSFUSIONS IN PATIENTS UNDERGOING ELECTIVE, NONCARDIAC, NONVASCULAR SURGERY

RETACRIT™ is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin >10 to ≤13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. RETACRIT™ is not indicated for patients who are willing to donate autologous blood preoperatively.

RETACRIT™ has not been shown to improve quality of life, fatigue, or patient well-being.

RETACRIT™ is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.