# Erythropoiesis Stimulating Agents Used in Chronic Kidney Disease
**September 2010**

## INTRODUCTION: [1-7]

Chronic Kidney Disease (CKD) is a multi-factorial condition affecting approximately 26 million American adults. CKD is most frequently caused by diabetes, hypertension, autoimmune disease, systemic infections, urinary tract infections, urinary stones, urinary tract obstruction, neoplasm, family history, recovery from acute kidney failure, reduced kidney mass, medications and low birth rate. Of note, diabetes and hypertension are conditions frequently encountered in the American Indian/Alaska Native (AI/AN) population. Approximately 16.3% of AI/AN adults have diagnosed diabetes and in some communities, more than 50% of adults are diabetic. Rates of end-stage renal disease (ESRD) in the AI/AN population are twice the rate of white Americans. Nearly 75% of ESRD cases in AI/AN patients are attributable to diabetes versus 40% in other racial groups. Prevalence rates vary across Indian country with a greater propensity in the southwestern regions, especially Arizona and New Mexico. In this geographic region, "the AI/AN rate was 6.5 times greater than the rate among whites."[7] Additionally, some data suggests a genetic link to renal disease in the AI/AN population. Cardiovascular disease is the leading cause of death in the AI/AN population as well as those patients with CKD.

FDA REMS[8]
In February 2010, the FDA approved a risk evaluation and mitigation strategy (REMS) to ensure safe use of the erythropoiesis stimulating agent (ESA) class of medications. This was in response to data that showed increase risk of tumor growth and a decrease in survival for patients with cancer who used ESAs. Additionally, data show the ESAs can increase the risk of MI, HF, stroke or blood clots. The goals for the ESA REMS 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 APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program.

The ESA REMS includes the dispensation of the ESA medication guide each time an ESA is dispensed to a patient or their representative, regardless of indication. For healthcare providers who use ESAs to treat non-cancer related anemia, enrollment in the APPRISE program is not required. For treatment of cancer related anemia with ESAs, the APPRISE program has specific requirements for healthcare providers and hospitals. These include:

- Healthcare providers who prescribe ESAs for patients with cancer must complete a training module over ESAs before being eligible for the APPRISE program (Note: "Healthcare providers not enrolled in the ESA APPRISE Oncology program will not be able to prescribe ESAs for use in patients with cancer.")

- Healthcare providers must attest to their understanding of the risks of using ESAs in cancer patients.
- Hospitals must be enrolled in the ESA APPRISE Oncology program to dispense ESAs.
- Hospitals must have a system in place to ensure that providers who prescribe ESAs for cancer patients have enrolled in the APPRISE program and comply with the program.
- Failure to comply with the APPRISE program could lead to suspension of access to ESA agents.

While much has been published recently concerning the use of ESAs in patients with cancer, this monograph will focus on the use of ESAs in patients with CKD.

## KEY QUESTIONS:

1. Are ESAs considered standard of care agents that should be used by a substantial proportion of the population with CKD related anemia?

2. What differences exist between each available agent related to adverse effects?

## PHARMACOLOGY/PHARMACOKINETICS: [9-12]

**Mechanism of Action:** ESAs stimulate erythropoiesis by the same mechanism as endogenous erythropoietin. Erythropoietin is produced from the kidney and released in response to hypoxia. ESAs stimulate the division and differentiation of progenitor cells, to induce reticulocyte release from the bone marrow, thereby increasing reticulocyte, Hg and Hct levels. Endogenous erythropoietin is impaired in CKD as erythropoietin deficiency is the underlying cause of this anemia. After administration, Hb levels begin to change in 2 to 6 weeks.

**Table 1: Pharmacokinetics of FDA Approved ESAs[10-12]**

| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| **Epoetin alfa (Epogen®, Procrit®)** | Peak: Hb level, 2-6 weeks | Vd: 9L<br>-Rapid in plasma, concentrated in liver, kidneys and bone marrow. | -Some degradation occurs<br>t1/2 (IV): 4-13 hours<br>t1/2 (subQ): 16-67 hours | Mainly excreted in feces with small amounts in urine. |
| **Darbepoetin alfa (Aranesp®)** | SubQ: slow absorption<br>Peak | Vd: 0.06 L/kg | t1/2 (IV): 21 hours<br>t1/2 (subQ): 46-70 hours<br>(dialysis/non-dialysis) | |

## FDA APPROVED INDICATIONS:[10-13]

**Epoetin alfa (Epogen®, Procrit®):**

- Treatment of anemia of chronic renal failure patients (dialysis and non-dialysis patients)
- Treatment of anemia of zidovudine-treated HIV-infected patients
- Treatment of anemia in cancer patients on chemotherapy

- Reduction of allogeneic blood transfusion in surgery patients

**Darbepoetin alfa (Aranesp®):**

- Anemia with chronic renal failure
- Anemia with non-myeloid malignancies due to chemotherapy

## CURRENT NATIONAL CORE FORMULARY ALTERNATIVES:[14]

Currently, the IHS National Core Formulary (NCF) does not contain an ESA.

## DOSAGE AND ADMINISTRATION (CKD):[10-13]

**Epoetin alfa (Epogen®, Procrit®):**

Chronic renal failure: IV (preferred for hemodialysis) or subcutaneous 50-100 units/kg 3 times weekly with dosing adjusted to target Hb of 10-12 g/dL

Maintenance Dose: median dose 75 units/kg 3 times/week (dialysis);
Non-dialysis dosing range: 75-150 units/kg/week

**Darbepoetin alfa (Aranesp®):**

Chronic renal failure: IV (preferred for hemodialysis) or subcutaneous weekly with dosing individualized to achieve and maintain a target of 10-12 g/dL

Initial dose: 0.45mcg/kg body weight (IV/SubQ); may use 0.75mcg/kg every 2 weeks in patients not on dialysis

Maintenance dose: individualize to achieve and maintain Hb 10-12 g/dL. For many patients, the maintenance dose will be lower than the starting dose.

**Table 2: Conversion:[13]**

| Previous Dosage of Epoetin alfa (units/week) | Adult Darbepoetin alfa dosage (units/week) |
|---|---|
| <1500 | 6.25 |
| 1500-2499 | 6.25 |
| 2500-4999 | 12.5 |
| 5000-10,999 | 25 |
| 11,000-17,999 | 40 |
| 18,000-33,999 | 60 |
| 34,000-89,999 | 100 |
| ≥90,000 | 200 |

**Note:** If epoetin alfa 2-3 times weekly, give darbepoetin alfa once weekly; if epoetin alfa once weekly, give darbepoetin alfa once every 2 weeks.

## GUIDELINES/SYSTEMATIC REVIEWS:

ERBP Position Statement[15]
The European Renal Best Practice (ERBP) Anemia Working Group recently released a position statement in response to the results of the Trial to Reduce Cardiovascular Events with Aranesp

Therapy (TREAT) Study. The TREAT Study (patients with CKD, diabetes and anemia) showed a similar rate of the primary cardiovascular composite end-point. However, patients with a history of stroke and assigned to the darbepoetin arm and with Hb target of 13 g/dL showed a higher risk of fatal or non-fatal stroke (secondary endpoint).[16] Based upon these data, the ERBP suggests:[15]

- Use caution when using ESAs in diabetic patients with CKD; a Hg target of 10-12 g/dL is suggested for diabetic patient with a history of stroke.
- A benefit versus risk assessment should be employed when using ESAs in diabetic patients with ischemic heart disease or previous history of stroke and should weigh the potential reduction in revascularization and transfusions.
- If using ESAs in patients with CKD and history of cancer, benefit versus risk should be assessed; if ESA is used, utilize the lowest possible dose.
- Do not start ESAs in iron-deficient patients before using iron replacement first.
- "In CKD patients, ESA treatment should be considered when Hb levels are consistently (i.e. measured twice at least 2 weeks apart) below 11 g/dL (possibly < 10 g/dL in patient with type 2 diabetes and with a history of strokes), and all other causes of anemia have been excluded; the threshold for treatment should be decided according to patient characteristics and symptoms, and the desired Hb target."

Of note, this is not considered a systematic review or guideline, but a guidance document in response to the TREAT Study (specifics to be discussed in more detail below).

In response to the results from the TREAT study, a retrospective, cross-sectional analysis was conducted and published by Imai and colleagues.[17] Data from over 7400 patients was reviewed to assess the incidence of symptomatic stroke and cancer in a Japanese CKD population. The results of this study revealed no significant change in symptomatic stroke or cancer for CKD patients using epoetin. It should be noted that this was a retrospective analysis and should be viewed as such.

KDOQI 2007[18]

Due to new data becoming available relative to the target Hb for CKD patients with anemia, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) workgroup met to discuss and modify its guidelines. These modifications include:

- Potential benefits and harms should be taken into consideration when selecting Hb target and when to initiate ESAs (expert opinion)
- For CKD patients on ESAs, a Hb target of 11-12 g/dL should be sought (expert opinion)
- For CKD patients on ESA, the Hb target should not be greater than 13 g/dL (evidence).

KDOQI[19]

In 2006, the National Kidney Foundation KDOQI Workgroup provided its second update to the clinical practice guidelines for the treatment of anemia in CKD. This guidance document provided evidence-based guidelines and clinical practice recommendations based upon expert opinion. Recommendations based upon strong to moderately strong evidence are noted, while expert opinion is discussed as recommendations. It is recommended that Hb testing should be assessed for all CKD patients and should be measured at least annually. Furthermore, the diagnosis of anemia should be made when the Hb is <13.5 g/dL in adult males and <12.0 g/dL for adult females. It is recommended (moderately strong) in CKD patients to keep Hb >11.0 g/dL, but there is insufficient evidence to keep Hb ≥13.0 for patients receiving ESAs. For patients receiving ESAs, it is recommended to test Hb at least monthly with ESA dosing to be determined by the Hb level. Based upon the data, Hb levels may increase by 0.7 to 2.5 g/dL in the first 4 weeks. These guidelines also discuss route and frequency of administration of ESAs. They recommend choosing the product/route based upon CKD stage,

treatment setting, efficacy, safety and class of ESA with subcutaneous route being favored on non-hemodialysis patients and IV route being favored in patients on hemodialysis based upon convenience. This document does not recommend one product over another and states that each is "effective in achieving and maintaining target Hb levels."

NICE[20]

In 2006, the National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGC-ACC) published their guideline for management of anemia in patients with CKD (note: NCGC-ACC is no longer active, but guidance is found via NICE). Similar to KDOQI, this guidance document addresses the detection, diagnosis and management of anemia associated with CKD. The workgroup discussed the importance of balancing stimulation of erythropoiesis and the provision of iron. Similar to the KDOQI recommendations, this document recommends choosing product based upon efficiency, patient comfort, frequency of administration, efficacy (subcutaneous vs. IV) and cost. The workgroup recommended the use of protocols that define roles and responsibilities in managing anemia of CKD and stressed the importance of educating patients on the importance of adherence with therapy. They also recommended considerations for patient preferences when prescribing ESAs (frequency, injection site pain, supply and storage requirements, etc.). They recommended offering ESA treatment to those "who are likely to benefit in terms of quality of life and physical function." From their review of the literature, they found no difference between erythropoietin alfa and darbepoetin for stable patients and no difference in efficacy between the two products. It was felt that pre-dialysis patients received the most long-term benefit from anemia correction. Dose and frequency of ESAs should keep the Hb increase between 1 – 2 g/dL/month. Contrary to the KDOQI recommendations, this guidance recommended keeping Hb between 10.5 and 12.5 g/dL. They recommended adjusting ESA dose when the Hb falls below 11.0 g/dL or above 12.0 g/dL. The workgroup recommended optimization of iron status before or with ESA initiation. The use of adjunctive ACE/ARB with ESAs was discussed related to the potential ESA resistance secondary to this combination. They found the evidence to be inconclusive for causation, but noted that an increased ESA dose should be considered. A detailed Hb maintenance algorithm was developed and included in this guidance document and would be worth consideration when treating anemia of CKD.

Cochrane

A 2005 Cochrane review was written by Cody and colleagues.[21] This systematic review of 15 clinical trials focused on the use of recombinant human erythropoietin in pre-dialysis CKD patients with anemia. Their findings were:

- Hb and Hct improvement in patients treated with erythropoietin
- Decreased number of blood transfusions in treated patients
- Improved quality of life and exercise capacity
- No data to support or refute ability of erythropoietin to affect renal disease progression or prevent dialysis.
- No significant increase in adverse events

Of note, this systematic review was published before the recent articles that brought the potential cardiovascular, stroke and cancer risks and it included data on pre-dialysis patients only.

ERBP/EBPG[22]

In 2004, the European Renal Best Practice/European Best Practice Guidelines (ERBP/EBPG) published an update to their 1999 document. Similar to previously discussed guidance documents, this guideline included both evidenced-based and expert opinion statements. Some of the recommendations associated with ESA use in anemia include:

- ESAs should be given to all CKD patients when Hb is consistently below 11 g/dL
- ESA route and frequency is dependent upon patient group (e g. dialysis), desired dose and specific product
- ESA dosing should be titrated to appropriate Hb level and should not exceed a rate of >2 g/dL per month
- Blood pressure should be closely monitored in CKD, especially during ESA initiation

**EFFICACY:**

In 2008 and 2010, Szczech and colleagues provided a secondary analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial.[23-25] To understand the implications of this analysis, it is important to have a background understanding of the original study. The CHOIR trial compared two different Hb targets (11.3 g/dL and 13.5 g/dL) for CKD patients with anemia and treated with epoetin-alfa. Its primary endpoint was a composite of death, MI, hospitalization for CHF and stroke. Quality of life (QOL) was also evaluated. The composite endpoint occurred with 125 events in the 13.5 g/dL group with 97 events in the 11.3 g/dL group (HR 1.34; 95% CI 1.03-1.74; p=0.03). QOL scores between groups were similar between groups. Therefore, the authors concluded that the higher target Hb "was associated with increased risk and no incremental improvement in the quality of life."[25]

The 2010 subgroup analysis focused on patients with diabetes and patients with heart failure (HF).[23] These patients were more likely to have additional comorbitities (cerebrovascular disease, CAD, PVD, atrial arrhythmias). No significant difference was seen for patients with HF and a higher target (46.3% vs. 50.8%, P=0.683), while the absence of HF and the use of a higher target was significant (HR=1.86; 95% CI 1.21-2.85; P=0.004). With diabetes, patients with baseline diabetes did not have a significant difference in the primary endpoint in the high target, while a trend was seen in non-diabetic patients with a higher target. These findings suggest additional research is needed and that certain subsets of population may have higher risks with the higher Hb target.

The 2008 subgroup analysis sought to compare the inability to achieve Hb targets and clinical outcomes.[24] At 4 months, they found that more patients in the 13.5 g/dL group failed to reach target as compared to the 11.3 g/dL group (37.5 vs. 4.7 %;, p<0.001). Additionally, they found that patients with a higher target required higher doses of epoetin alfa (35.1 vs. 9.6%, p < 0.001). Findings at 9 months were similar to 4 months. The authors concluded that higher epoetin alfa doses were associated with worse outcomes when higher targets were used and that patients that achieved the higher target Hb had better outcomes than those who did not. While specific information cannot be taken from this subgroup analysis, these data are hypothesis generating.

Pfeffer and colleagues published results from the TREAT trial in 2009.[16] This clinical trial randomized patients to receive treatment with darbepoetin alfa with a target of 13 g/dL or placebo. The primary endpoints were time to the composite of death or cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for MI) and time to composite of death or end-stage renal disease. Study groups were similar except for HF history (darbepoetin 31.5% vs. placebo 35.2%, P=0.01). A trend for the primary cardiovascular composite outcome was seen (31.4% vs. 29.7%; HR 1.05; 95% CI, 0.94-1.17; P=0.41) as well as death or end-stage renal disease (HR 1.06; 95% CI, 0.95-1.19, P=0.29). A statistically significant difference in fatal or nonfatal stroke was seen (5% darbepoetin, 2.6% placebo; HR 1.92; 95% CI, 1.38-2.68; p <0.001). No difference was seen with respect to cancer related adverse

events (6.9% vs. 6.4%, p=0.53). Essentially, it was found that darbepoetin alfa was associated with an increased risk of stroke in patients with diabetes, CKD and anemia.

Ritz and colleagues published the results of the Anemia Correction in Diabetes (ACORD) trial in 2007.[26] This study included patients with diabetes (type 1 or 2), mild to moderate anemia and stage 1 to 3 CKD. Patients were randomized to a target Hb of 13-15 g/dL (group 1) or 10.5-11.5 g/dL (group 2). Group 1 patients received epoetin beta dosed to reach target and group 2 patients received epoetin beta when Hb fell below 10.5 g/dL for 2 consecutive weeks or when it fell below 10 g/dL. The primary endpoint for this study was change in left ventricular mass index (LVMI), while echocardiography data, renal function, QOL and safety were included as secondary endpoints. There were no statistically significant differences in LVMI at baseline, 6 months and 15 months. Echocardiography data revealed no significant changes between groups throughout the study. No difference was seen relative to renal function or adverse events, but group 1 had a significant improvement in QOL scores (P= 0.04).

The results of the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial were published by Drüeke et al. in 2006.[27] Patients with stage 3/4 CKD and mild to moderate anemia were randomized to a target Hb of 13-15 g/dL (group 1) or 10.5-11.5 g/dL (group 2). Epoetin beta was administered to group 1 patients and in group 2 patients when Hb fell below 10.5 g/dL. The primary endpoint was a composite of cardiovascular events (sudden death, MI, acute HF, stroke, TIA, angina leading to hospitalization, PVD complication or cardiac arrhythmia requiring hospitalization), while secondary endpoints were LVMI, QOL, and CKD progression. Other than weight and use of beta-blockers, each group was equally matched at baseline. No difference was detected for the primary endpoint between groups (HR 0.78; 95% CI, 0.53-1.14; adjusted P=0.20). Group 1 required dialysis more frequently than group 2 (P=0.03). The authors concluded the in patients with CKD, treatment to Hb 13-15 g/dL did not reduce the risk of cardiovascular events.

Iseki and colleagues published data from a retrospective analysis of Japanese dialysis patients in 1996.[28] They analyzed and compared data pre-erythropoietin and post-erythropoietin to determine the effect of erythropoietin us on cardiovascular disease. This study revealed an increase in stroke (OR 1.22, 95% CI 1.06-1.41, P <0.001) and an increase in MI (OR 1.87; 95% CI 1.66-2.10, P <0.01). Since this was a retrospective analysis of registry data, it should be viewed as hypothesis generating.

## ADVERSE EVENTS:[10-13]

### Epoetin alfa (Epogen®, Procrit®):

**>10%:**

**Cardiovascular:** Hypertension (5% to 24%), thrombotic/vascular events (coronary artery bypass graft surgery: 23%), edema (6% to 17%), deep vein thrombosis (≤11%)

**Central nervous system:** Fever (29% to 51%), dizziness (5% to 21%), insomnia (13% to 21%), headache (10% to 19%)

**Dermatologic:** Pruritus (14% to 22%), skin pain (4% to 18%), rash (≤16%)

**Gastrointestinal:** Nausea (11% to 58%), constipation (42% to 53%), vomiting (8% to 29%), diarrhea (6% to 21%), dyspepsia (7% to 11%)

**Genitourinary:** Urinary tract infection (3% to 12%)

**Local:** Injection site reaction (<10% to 29%)

**Neuromuscular & skeletal**: Arthralgia (≤11%), paresthesia (≤11%)

**Respiratory:** Cough (≤18%), congestion (≤15%), dyspnea (13% to 14%), upper respiratory infection (≤11%)

**1% to 10%:**

**Central nervous system**: Seizure (1% to 3%)
**Local:** Clotted vascular access (7%)

**Darbepoetin alfa (Aranesp®):**

**>10%**
**Cardiovascular:** Edema (21%), hypertension (4% to 20%), hypotension (20%)
**Central nervous system:** Fatigue (9% to 33%), fever (4% to 19%), headache (12% to 15%), dizziness (7% to 14%)
**Gastrointestinal:** Diarrhea (14% to 22%), constipation (5% to 18%), vomiting (2% to 14%), nausea (11%)
**Neuromuscular & skeletal:** Muscle spasm (17%), arthralgia (9% to 13%)
**Respiratory:** Upper respiratory infection (15%)
**Miscellaneous:** Infection (24%)

**1% to 10%:**

**Cardiovascular:** Peripheral edema (10%), arrhythmia/arrest (8%), angina/chest pain (7% to 8%), fluid overload (6%), thrombosis (6%), CHF (5%), MI (2%)
**Central nervous system:** Stroke (2% to 5%), seizure (≤1%), TIA (≤1%)
**Dermatologic:** Rash (7%), pruritus (6%)
**Endocrine & metabolic:** Dehydration (3% to 5%)
**Gastrointestinal:** Abdominal pain (10%)
**Local:** Vascular access hemorrhage (7%), injection site pain (6%), vascular access infection (6%), vascular access thrombosis (6%)
**Neuromuscular & skeletal**: Limb pain (8%), myalgia (8%), back pain (7%), weakness (5%)
**Respiratory:** Dyspnea (2% to 10%), cough (9%), bronchitis (5%), pneumonia (3%), pulmonary embolism (1%)
**Miscellaneous:** Flu-like syndrome (6%)

## PRECAUTIONS/CONTRAINDICATIONS:[10-13]

**Black Box Warning:** [10-13]
Increased mortality, serious cardiovascular events, thromboembolic events, stroke and increased risk of tumor progression or recurrence

Chronic Renal Failure:

- In clinical studies, patients experienced greater risks of death, serious cardiovascular events and stroke when administered ESAs to target Hb levels of 13 g/dL and above.
- Individualized dosing to achieve and maintain Hb levels within the range of 10-12 g/dL.

Cancer: (included for completeness)

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in 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 cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp® 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.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

**Epoetin alfa (Epogen®, Procrit®):**

- Uncontrolled hypertension (Contraindication)
- Known hypersensitivity to mammalian cell-derived products (Contraindication)
- Known hypersensitivity to albumin (human) (Contraindication)
- Safety and efficacy in underlying hematologic disease not established for patients with a history of seizure or underlying hematologic disorder (e.g., sickle cell anemia, myelodysplastic syndromes or hypercoagulable disorders)
- Use caution in patients with known porphyria
- Increased rate of DVT in patients not receiving anticoagulant prophylaxis, therefore consider DVT prophylaxis in surgical patients.

**Darbepoetin alfa (Aranesp®):**

- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients
- Safety and efficacy in underlying hematologic disease not established for patients with a history of seizure or underlying hematologic disorder (e.g., porphyria, thalassemia, hemolytic anemia, sickle cell anemia)
- Increased mortality seen in perisurgical CABG patients who received epoetin

## LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL:[13, 29]

**Epoetin alfa (Epogen®, Procrit®):**

Epoetin alfa-darbepoetin alfa, epoetin beta
Epogen®-Neupogen®

**Darbepoetin alfa (Aranesp®):**

Aranesp®-Aralast; Aricept®
Darbepoetin alfa-dalteparin, epoetin alfa, epoetin beta

## DRUG INTERACTIONS:[10-13]

There are no known drug interactions for these products.

## SPECIAL NOTES:[30-32]

Each of the ESAs listed have FDA-approved patient medication guides that must be dispensed with each new prescription and refill as required via the REMS.

## CONCLUSIONS:

1. Are ESAs considered standard of care agents that should be used by a substantial proportion of the population with CKD?

   In the recent past, ESAs were frequently employed to treat CKD related anemia and would possibly have been considered standard of care. However, in light of the release of the TREAT study and guidance from the FDA, it appears that ESA place in therapy is more in question. Some guidance/position statements have been performed and recommend a discussion of benefit versus risk for using ESAs in CKD related anemia. They also recommend using ESAs with caution if patients have certain characteristics such as cancer, diabetes with ischemic heart disease or history of stroke.

2. What differences exist between each available agent related to adverse effects?

   These three agents appear to be relatively similar with respect to adverse effects. As noted, a primary concern is the potential class effect and the subsequent black box warning associated with the use of ESAs and the corresponding increased risk of mortality, serious cardiovascular events, thromboembolic events, stroke and tumor progression/recurrence (in cancer patients).

## RECOMMENDATIONS:

Based upon this information, it seems that the ESA class of medications does not fit the usual NPTC criteria for inclusion on the NCF. While there still appears to be a place in therapy for the ESAs, it seems most reasonable to keep the decision a local one, level rather than a national level decision. It also seems important to stress the importance of careful patient selection when utilizing this class of medications and following the FDA recommendations for use of these agents.

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