Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Decision Summary

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, reduced survival) have prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). The initial scope of this national coverage analysis (NCA) was "non-renal" uses. Current non-renal indications for ESA use that are approved by the FDA are: cancer treatment related anemia (erythropoietin, darbepoetin), AZT-induced anemia in HIV-AIDS (erythropoietin only), and prophylactic use for select patients undergoing elective orthopedic procedures with significant expected blood loss (erythropoietin only) (Aranesp® drug label; Procrit® drug label). Because there is a preponderance of emerging data for ESA use in the oncology setting, the focus of the NCA will be ESA use in cancer and related conditions. The other non-renal uses may be addressed in future NCAs. We expect that our future reviews will also include the more adequately powered study of ESA use in spine surgery patients. In the interim, local Medicare contractors may continue to make reasonable and necessary determinations on all non-cancer and non-neoplastic conditions as well as other non-renal uses of ESAs.

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. the anemia of myelodysplasia
3. the anemia of myeloid cancers
4. the anemia associated with the treatment of myeloid cancers or erythroid cancers
5. the anemia of cancer not related to cancer treatment
6. any anemia associated with radiotherapy
7. prophylactic use to prevent chemotherapy-induced anemia
8. prophylactic use to reduce tumor hypoxia
9. patients with erythropoietin-type resistance due to neutralizing antibodies
10. patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
11. patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
12. anemia due to cancer treatment if patients have uncontrolled hypertension
13. patients with thrombotic episodes related to malignancy

				article 2005
	Breast	Epo α	Rosenzweig	Yes, 2004
Immunotherapy	Colon	Darbe α	Unknown	No
Radiotherapy	Head-neck	Darbe α	Danish Head & Neck Cancer 10 Study Group	No
	Head-neck	Epo α	Machtay	No
	Head-neck	Epo ß	Henke	Yes, 2003
	Head-neck	Epo α	Johnson & Johnson EPO-GBR-7	No Reportedly terminated bc of slow enrollment at 301 of 800 in 2002. 5 yr f/u pending.
Chemo-Radiotherapy	Gastric/Rectal	Epo α	Vadhan-Raj PR00or1-03-006	No
	Cervical	Epo α	Unspecified investigators for investigator initiated protocol Johnson & Johnson PR01-04-005/GOG-0191	No
	Lung (small cell)	Epo α	Wright Johnson & Johnson EPO-CAN-15	Yes, 2007
None	Lung (non-small cell)	Epo α	Unknown	No
None	Assorted	Darbe	Unknown	No

Tx= treatment Epo= erythropoietin Darb= darbepoetin bc= because fu= follow-up

Non-small Cell Lung Cancer, Receiving Chemotherapy, Pegylated Erythropoietin ß (Hoffmann-LaRoche Funding) (FDA Alert)

A prospective, 4-arm, dose-finding trial was conducted in anemic Stage III or IV non-small cell lung cancer patients undergoing first-line chemotherapy. Pegylated erythropoietin was titrated to achieve hemoglobin levels between 11 and 13 g/dl. The study was terminated after enrollment of 153 patients because of increased mortality in the experimental treatment arms.

	ß	AGO Ovarian Cancer Study Group		(Reportedly still recruiting)	
Head-neck	Epo	P Lambin EORTC 229996-24002	Loco-regional control Overall survival	1999	
Head-neck	Epo α	JS Stewart	Local tumor control Disease-free survival Overall survival	1999	
Head-neck LOOK	Epo α	Cross Canada Institute Parliament	Local tumor control Overall survival	Not known	
Lung	Epo α	M 'Brien	Response to chemotherapy	1998	
Lung (non-small cell)	Epo	AR Blackstock	Tumor response rate Overall survival	2002	
Lung (small cell)	Darb α	Amgen 20010145	Survival time	2002 No longer recruiting	NCT00119613[f]
Pelvic	Epo α	D Antonadou	Disease-free survival	Not known # #	
Leukemia (chronic lymphocytic)	Darb α	M Hallek German CLL Study Group	Multiple endpoints including survival	2004	NCT00281892[g]
Lymphoma (large B-cell)	Darb α	A Bosley/R Delarue Group d'Etude des Lymphomes de l'Adulte FR-2003-3005 GELA LNH03-6B	Event-free survival	2003 Expected completion 2008	Phase 4 Due 8/1010* NCT00144755[h]

*It should be noted that this study is being conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival

**Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I, Munzel K. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer. 2007;March 9 E-pub.

For patients undergoing treatment for these cancers, we propose that ESA use is reasonable and necessary with the following limitations:

1. the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be < 9 g/dl/27% in patients without known cardiovascular disease and < 10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae).
2. the maximum covered treatment duration is 12 weeks/year;
3. the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 Î¼g for darbepoietin;
4. continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise < 1 g/dl/< 3%) after 4 weeks of treatment;
5. continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and
6. continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit > 1 g/dl/> 3% after 2 weeks of treatment.

Local contractors may continue to make reasonable and necessary determinations for all uses of ESA therapy for beneficiaries with cancer whose condition is not addressed above.

We are requesting public comments on this proposed determination pursuant to section 1862 as revised by 731 of the Medicare Modernization Act. In light of the issues discussed in our review of the evidence and serious safety concerns voiced in the May 10, 2007 FDA Oncologic Drugs Advisory Committee (ODAC) meeting we are also interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Appendices

Bibliography

Abel R. Use of recombinant human erythropoietin in the treatment of anemia in patients who have cancer. Seminars in Oncology. 1992;19 (No 3 Suppl 8):29-35.