



**Related MLN Matters Article #:** MM5818 **Revised**

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### *Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions*

#### **Key Words**

MM5818, CR5818, R80NCD, R1413CP, ESA, Cancer, Neoplastic

#### **Provider Types Affected**

Providers and suppliers who bill Medicare Carriers, Fiscal Intermediaries (FIs), Regional Home Health Intermediaries (RHHIs), Part A/B Medicare Administrative Contractors (A/B MACs) and Durable Medical Equipment MACs (DME MACs) for administering or supplying ESAs for cancer and related neoplastic conditions to Medicare beneficiaries

**Note:** MLN Matters article MM5818 was revised on April 25, 2008, to correctly state the requirement for "Maintenance of ESA therapy" (See page 2 bullet in **bold**). It should have stated that the "starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is  $\geq$  1g/dL (hematocrit  $\geq$  3%)."

#### **Key Points**

- The effective date of the instruction is July 30, 2007.
- The implementation date is April 7, 2008.
- Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, and reduced survival) derived from clinical trials in several cancer and non-cancer populations prompted the Centers for Medicare & Medicaid Services (CMS) to review its coverage of ESAs.
- On March 14, 2007, CMS opened a National Coverage Analysis to evaluate the uses of ESAs in non-renal disease applications. On July 30, 2007, CMS issued a Decision Memorandum specifically narrowed to the use of ESAs in cancer and other neoplastic conditions.

### Reasonable and Necessary ESA Use

- CMS has determined that ESA treatment for the anemia secondary to a regimen of myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia is reasonable and necessary only under the following specified conditions:
  - The hemoglobin level immediately prior to the first administration is < 10 g/dL (or the hematocrit is < 30%). The hemoglobin level prior to any maintenance administration is < 10g/dL (or the hematocrit is < 30%);
  - The starting dose for ESA treatment is up to either of the recommended Food and Drug Administration (FDA) approved label starting doses for cancer patients receiving chemotherapy, which includes the 150 U/kg/3 times weekly or the 40,000 U weekly doses for epoetin alfa and the 2.25 mcg/kg/weekly or the 500 mcg once every three week dose for darbepoetin alpha;
  - **Maintenance of ESA therapy is the starting dose if the hemoglobin level remains below 10 g/dL (or hematocrit is < 30%) 4 weeks after initiation of therapy and the rise in hemoglobin is  $\geq$  1g/dL (hematocrit  $\geq$  3%);**
  - For patients whose hemoglobin rises <1 g/dl (hematocrit rise < 3%) compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains <10 g/dL after 4 weeks of treatment (or the hematocrit is < 30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises < 1 g/dl (hematocrit rise < 3%) compared to pretreatment baseline by 8 weeks of treatment;
  - Continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin > 1 g/dl (hematocrit > 3%) over any 2 week period of treatment unless the hemoglobin remains below or subsequently falls to < 10 g/dL (or the hematocrit is < 30%). Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previously administered dose; and
  - ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen.

### Not Reasonable and Necessary ESA Use

- Either because of a deleterious effect of ESAs on the underlying disease, or because the underlying disease increases the risk of adverse effects related to ESA use, CMS has also determined that ESA treatment is not reasonable and necessary for beneficiaries with the following clinical conditions:
  - Any anemia in cancer or cancer treatment patients due to folate deficiency (diagnosis code 281.2), B-12 deficiency (281.1 or 281.3), iron deficiency (280.0-280.9), hemolysis (282.0, 282.2, 282.9, 283.0, 283.2, 283.9, 283.10, 283.19), bleeding (280.0 or 285.1), or bone marrow fibrosis;
  - Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML) (205.00-205.21, 205.80-205.91), or erythroid cancers (207.00-207.81);
  - Anemia of cancer not related to cancer treatment;
  - Any anemia associated only with radiotherapy;
  - Prophylactic use to prevent chemotherapy-induced anemia;

- Prophylactic use to reduce tumor hypoxia;
- Erythropoietin-type resistance due to neutralizing antibodies; and
- Anemia due to cancer treatment if patients have uncontrolled hypertension.

### Claims Processing

- Effective for claims with dates of service on or after January 1, 2008, Medicare will deny non-end-stage renal disease (ESRD) ESA services for J0881 or J0885 when:
  - Billed with modifier EC (ESA, anemia, non-chemo/radio) when a diagnosis on the claim is present for any anemia in cancer or cancer treatment patients due to folate deficiency (diagnosis code 281.2), B-12 deficiency (281.1 or 281.3), iron deficiency (280.0-280.9), hemolysis (282.0, 282.2, 282.9, 283.0, 283.2, 283.9, 283.10, 283.19), bleeding (280.0 or 285.1), anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML) (205.00-205.21, 205.80-205.91), or erythroid cancers (207.00-207.81);
  - Billed with modifier EC for any anemia in cancer or cancer treatment patients due to bone marrow fibrosis, anemia of cancer not related to cancer treatment, prophylactic use to prevent cancer-induced anemia, prophylactic use to reduce tumor hypoxia, erythropoietin-type resistance due to neutralizing antibodies, and anemia due to cancer treatment if patients have uncontrolled hypertension;
  - Billed with modifier EA (ESA, anemia, chemo-induced) for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia when a hemoglobin 10.0g/dL or greater or hematocrit 30.0% or greater is reported; or
  - Billed with modifier EB (ESA, anemia, radio-induced).

### Process for Denials

- Denial of claims for non-ESRD ESAs for cancer and related neoplastic indications as outlined in National Coverage Determination (NCD) 110.21 are based on reasonable and necessary determinations.
- A provider may have the beneficiary sign an Advance Beneficiary Notice (ABN), making the beneficiary liable for services not covered by Medicare.
- When denying ESA claims, Medicare contractors will use Medicare Summary Notice 15.20: "*The following policies [NCD 110.21] were used when we made this decision*", and remittance reason code 50: "*These are non-covered services because this is not deemed a 'medical necessity' by the payer.*"
- However, standard systems will assign liability for the denied charges to the provider unless documentation of the ABN is present on the claim. Denials are subject to appeal and standard systems will allow for medical review override of denials. Contractors may reverse the denial if the review results in a determination of clinical necessity.
- Medicare contractors have discretion to establish local coverage policies for those indications not included in NCD 110.21.

**Note:** This addition/revision of Section 110.21 of Pub.100-03 is an NCD. NCDs are binding on all carriers, FIs, quality improvement organizations, qualified independent contractors, the Medicare Appeals Council, and administrative law judges (ALJs) (See 42 Code of Federal Regulations, Section 405.1060(a)(4) (2005)). An NCD that expands coverage is also binding on a Medicare advantage organization. In addition, an ALJ may not review an NCD (See section 1869(f)(1)(A)(i) of the Social Security Act).

- Medicare contractors will not search files to retract payment for claims paid prior to April 7, 2008, but will adjust claims brought to their attention.

## Important Links

The related MLN Matters article can be found at

<http://www.cms.hhs.gov/MLNMattersArticles/downloads/MM5818.pdf> on the CMS website.

The official instruction (CR5818) was issued in two transmittals. The first is the NCD transmittal and that is available at <http://www.cms.hhs.gov/Transmittals/downloads/R80NCD.pdf> on the CMS website. The second transmittal revises the *Medicare Claims Processing Manual* and it is at

<http://www.cms.hhs.gov/Transmittals/downloads/R1413CP.pdf> on the CMS website

If providers have any questions, they may contact their Medicare contractor at their toll-free number, which may be found at <http://www.cms.hhs.gov/MLNProducts/downloads/CallCenterTollNumDirectory.zip> on the CMS website.