ERYTHROPOIESIS STIMULATING AGENTS (ESAs) THERAPY POLICY

Policy:

I. Precertification Criteria

For Aranesp, Procrit, Epogen

A documented diagnosis of one of the following:

A. Anemia from myelodysplastic syndrome; or
B. Anemia of prematurity; or
C. Special circumstance members who will not or can not receive whole blood or components as replacement for traumatic or surgical loss; or
D. Treatment of anemic members scheduled to undergo high-risk surgery who are at increased risk of or intolerant to transfusions; or
E. Treatment of anemia associated with chronic renal failure, whether or not on dialysis; or
F. Treatment of anemia in members receiving chemotherapy for hepatitis C; or
G. Treatment of anemia of chronic disease other than cancer when an underlying chronic disease associated with anemia has been identified (see appendix); or
H. Treatment of anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphomas and lymphocytic leukemia; or
I. Treatment of anemia due to zidovudine in HIV-infected members.

For Mircera

A. A documented diagnosis of anemia associated with chronic kidney disease in persons on dialysis and persons not on dialysis.

Note: Omontys has been removed from the market

Specific Criteria for Erythropoietin and Darbepoietin Therapy:

Criteria for Initiation of Therapy:

1. For treatment of anemia associated with myelosuppressive anticancer chemotherapy:
   a. Erythropoiesis stimulating agents (ESAs) are considered medically necessary where hemoglobin (Hgb) has fallen below 10g/dL and the following criteria are met:
      i. Anemia is secondary to myelosuppressive anticancer chemotherapy for solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia; and
      ii. Adequate iron stores have been demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum transferrin saturation (TSAT greater than 20%) within the prior 12 months (Note: For persons with iron deficiency, ESAs may be initiated simultaneously with iron replacement), and
      iii. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
      iv. ESAs intended to decrease the need for transfusions in persons who will receive chemotherapy for a minimum of 2 months.
b. Providers must confirm compliance and participation in the REMS program that has been implemented for ESA being used in cancer; and
c. The starting dose of ESAs are equal to the following, based upon FDA labeling, or comparable fixed dosing schedules:
   i. Erythropoietin: 150 units/kg 3 times per week, or 40,000 units weekly in adults; 600 units/kg (maximum 40,000 units) weekly for children.
   ii. Darbepoetin: 2.25 mcg/kg per week, or 500 mcg every 3 weeks.

2. For treatment of anemia associated with myelodysplastic syndrome, ESAs are considered medically necessary where hemoglobin (Hgb) has fallen below 10g/dL, and the following criteria are met:
   a. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency, ESAs may be initiated simultaneously with iron replacement), and
   b. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
c. Bone marrow has less than 15% blasts, and
d. Member has required transfusion of 2 or fewer units of blood per month, and
e. Endogenous serum erythropoietin (EPO) levels are less than or equal to 500 IU/L.

3. For treatment of anemia associated chronic renal failure on dialysis:
   a. ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:
      i. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
      ii. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
   b. The starting dose is equal to the following, based upon FDA labeling, or comparable fixed dose schedules:
      i. Erythropoietin: 50 to 100 units/kg body weight 3 times per week for adults; 50 units/kg body weight for children.
      ii. Darbepoetin: 0.45 mcg/kg body weight once-weekly or 0.75 mcg/kg body weight every 2 weeks.

4. For treatment of anemia associated chronic renal failure not on dialysis:
   a. ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:
      i. Member has chronic kidney failure (defined as creatinine clearance less than 60 ml/min, or glomerular filtration rate (GFR) less than 60 ml/min/1.73 m²); and
      ii. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
      iii. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
      iv. The rate of hemoglobin decline indicates the likelihood of requiring a red blood cell (RBC) transfusion; and
Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

b. The starting dose is equal to the following, based upon FDA labeling, or comparable fixed dose schedules:
   i. Erythropoietin: 50 to 100 units/kg body weight 3 times per week for adults; 50 units/kg body weight for children.
   ii. Darbepoetin: 0.45 mcg/kg body weight once-weekly or 0.75 mcg/kg body weight every 2 weeks.

5. For treatment of anemia related to zidovudine in HIV-infected persons, ESAs are considered medically necessary where hemoglobin (Hgb) is less than 10 g/dL, and the following criteria are met:
   a. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/ml) or serum iron saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
   b. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
   c. Endogenous EPO level is less than or equal to 500 IU/L; and
   d. Dose of zidovudine is less than or equal to 4200 mg/week.

6. For treatment of anemia due to chemotherapy (e.g., ribavirin) in persons with hepatitis C, ESAs are considered medically necessary where the Hgb is less than 10 g/dL and the following criteria are met:
   a. Member is receiving interferon or pegylated interferon plus ribavirin; and
   b. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
   c. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia; and
   d. Hgb remains below 10 g/dl despite reduction of dose or ribavirin (dose of ribavirin can be decreased by 80 percent of target dose; daily ribavirin dose should not be less than 800 mg).

7. For treatment of anemia of chronic disease other than cancer, ESAs are considered medically necessary where Hgb is less than 10 g/dL and the following criteria are met:
   a. An underlying chronic disease has been identified; and
   b. Adequate iron stores are demonstrated by means of bone marrow iron or serum ferritin levels (greater than 100 ng/dl) or serum transferrin saturation (TSAT greater than 20%) within the past 12 months (Note: For persons with iron deficiency on dialysis, ESAs may be initiated simultaneously with iron replacement); and
   c. Member is exhibiting symptoms of anemia (such as fatigue, weakness, shortness of breath, or lightheadedness) affecting their ability to perform activities of daily living, or the member exhibits angina, syncope, or tachycardia from the anemia.

8. For treatment of anemic members scheduled to undergo high-risk surgery at increased risk of or intolerant to transfusions, ESAs are considered medically necessary in persons with a Hgb less than 13 g/dL.

9. For treatment of anemia of prematurity, ESAs are considered medically necessary when the member has either a birth weight of less than 1,500 grams or a gestational age of less than 33 weeks (medically necessary duration of therapy limited to 6 weeks).

10. For special circumstance members who will not or can not receive whole blood or components as replacement for traumatic or surgical loss, ESAs are considered medically necessary in persons with a Hgb less than 12 g/dL.
AUTHORIZATION PERIOD AND LIMITATIONS

Initial approval:
- for MDS, chemotherapy: 3 months
- for chronic kidney disease: 4 months
- for all other indications: 8 weeks

Reauthorizations/Extended Approvals:

Criteria for continuation of chronic ESAs in persons with anemia due to myelosuppressive anticancer chemotherapy
A. The maintenance dose of ESAs are equal to the starting dose if: (i) the hemoglobin remains below 10 g/dL 4 weeks after initiation of therapy; and (ii) the rise in hemoglobin is greater than or equal to 1 g/dL;
B. Continued administration of ESAs are considered not medically necessary if there is a rapid rise in hemoglobin greater than 1 g/dl over 2 weeks of treatment unless the hemoglobin remains below or subsequently falls to less than 10 g/dL. Continuation and reinstatement of ESA therapy must include a dose reduction of 25% for epoetin and 40% for darbepoetin from the previously administered dose.
C. For persons whose hemoglobin rises less than 1 g/dl compared to pretreatment baseline over 4 weeks of treatment and whose hemoglobin level remains less than 10 g/dL after the initial 4 weeks of treatment (for epoetin) or 6 weeks of treatment (for darbepoetin), the dose may be increased as follows:
   - For epoetin: 300 units/kg three times weekly or 60,000 units weekly in adults; 900 units/kg (maximum 60,000 units) weekly in children.
   - For darbepoetin: 4.5 mcg/kg weekly. No dose adjustment is recommended if the dose is given every 3 weeks.
D. Continued use of ESAs are considered not medically necessary if the hemoglobin rises less than 1 g/dl compared to pretreatment baseline by 8 weeks of treatment.

Criteria for continuation of chronic ESAs for chronic renal failure on dialysis
A. ESAs should be administered with a Hgb range of 10 g/dL to 11 g/dL (Note: maintenance at a higher Hgb level may be necessary for persons with acute myocardial infarction, angina, orthostatic hypotension, living at an elevation of greater than 6000 feet, or anemia with Hgb below 11 g/dL has significantly interfered with activities of daily living). If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESAs, and use the lowest dose of ESAs sufficient to reduce the need for RBC transfusions.
B. If the hemoglobin rises by more than 1 g/dL in any 2 week period, reduce the dose of epoetin or darbepoetin by 25% or more as needed to reduce the rapid response.
C. If the hemoglobin does not increase by more than 1 g/dL after 4 weeks of therapy, the dose of epoetin or darbepoetin may be increased by 25%.
D. Increases in dose should not occur more often than once every 4 weeks. Doses may be decreased more frequently. Patients who do not respond after 12 weeks of dose escalation are unlikely to respond to additional dose adjustments.

Criteria for continuation of chronic ESAs for chronic renal failure not on dialysis
A. If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESAs, and use the lowest dose of ESAs sufficient to reduce the need for RBC transfusions.
B. If the hemoglobin rises by more than 1 g/dL in any 2 week period, reduce the dose of epoetin or darbepoetin by 25% or more as needed to reduce the rapid response.
C. If the hemoglobin does not increase by more than 1 g/dL after 4 weeks of therapy, the dose of epoetin or darbepoetin may be increased by 25%.
D. Increases in dose should not occur more often than once every 4 weeks. Doses may be decreased more frequently. Patients who do not respond after 12 weeks of dose escalation are unlikely to respond to additional dose adjustments.
Criteria for continuation of chronic ESAs for other indications
A. For persons who meet medical necessity criteria for ESAs, continued ESAs are considered medically necessary for persons with a Hgb less than 11 g/dL. (For anemic members scheduled to undergo high-risk surgery, continued ESAs are considered medically necessary where Hgb is less than 13 g/dL).

Discontinuation criteria for ESAs
A. For indications other than end-stage renal disease, continued ESAs are considered not medically necessary if the member's Hgb has failed to rise by 1 g/dL compared to pre-treatment baseline within 8 weeks of therapy despite appropriate dose escalation.
B. Continued ESAs are considered not medically necessary for myelodysplastic syndrome if transfusion requirements have been reduced by less than 50% after 6 months of therapy.
C. ESAs for each course of chemotherapy for anemic persons with cancer or hepatitis C includes the 8 weeks following the final dose of chemotherapy in a chemotherapy regimen.

NON-COVERAGE
Erythropoiesis stimulating agent (ESA) therapy is considered experimental/investigational and/or NOT medically necessary and is NOT covered for the following conditions:
a) Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
b) Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers
c) Anemia of cancer not related to cancer treatment
d) Untreated myeloid diseases
e) Any anemia associated only with radiotherapy
f) Prophylactic use to prevent chemotherapy-induced anemia
g) Prophylactic use to reduce tumor hypoxia
h) Patients with erythropoietin-type resistance due to neutralizing antibodies
i) Anemia due to cancer treatment if patients have uncontrolled hypertension
j) Any iron deficiency anemia
k) Any megaloblastic anemia
l) Any hemolytic anemia
m) Blood loss
n) Any other causes of anemia
o) Treatment of dysautonomia with chronic orthostasis
p) Anemia secondary to thalassemia minor

REFERENCES

Disclaimer: Coventry Health Care, Inc. (CHC) medical policies, technology assessments, and medical reviews (collectively “CHC Policies”) are developed by CHC to provide guidance in administering plan benefits and constitute neither offers of coverage nor medical advice. Access to CHC Policies is provided for general reference purposes only and does not infer guaranteed coverage. CHC does not provide health care services or supplies. Providers are expected to exercise their independent medical judgment in rendering the most appropriate care. State and federal law, as well as benefit plan terms and conditions and CHC Policies in effect on the date that any service is rendered, including but not limited to definitions and specific inclusions/exclusions, take precedence over clinical policy and must be considered first in determining eligibility for coverage. The terms of the member's benefit plan shall determine coverage. Some benefit plans exclude coverage for services or supplies that Coventry may consider medically necessary. If there is a discrepancy between this policy and a member's benefit plan, the benefits shall govern. Coverage may also differ for CHC Medicare and/or Medicaid members based on any applicable Centers for Medicare & Medicaid Services (CMS) coverage statements including National Coverage Determination (NCD), Local Medical Review Policies (LMRP), and/or Local Coverage Determinations (LCD). As clinical technology is continually updated, CHC policies are subject to periodic updates. Do not rely on printed versions of CHC policies as they may be outdated. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or means without the written consent of CHC.