RxAdvance

Clinical Policy Title:	epoetin alfa, epoetin alfa-epbx
Policy Number:	RxA.265
Drug(s) Applied:	Epogen®, Procrit®, Retacrit®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All line of business

Background

The following are erythropoiesis-stimulating agents (ESAs) requiring prior authorization: epoetin alfa (Epogen® and Procrit®) and epoetin alfa-epbx (Retacrit®). ESAs are indicated for:

- Treatment of anemia due to:
  - Chronic kidney disease (CKD) in patients on dialysis and not on dialysis.
  - Zidovudine in patients with human immunodeficiency virus -infection.
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

Limitation(s) of use:

- ESAs have not been shown to improve quality of life, fatigue, or patient well-being.
- ESAs are 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
epoetin alfa (Epogen®, Procrit®) epoetin alfa-epbx (Retacrit®)	Anemia due to chronic kidney disease	Initial dose: 50 to 100 Units/kg three times weekly (adults) intravenously or subcutaneously and 50 Units/kg three times weekly (children on dialysis) intravenously or subcutaneously.	Varies depending on indication and frequency of administration

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		Individualize maintenance dose. Intravenous route is recommended for patients on hemodialysis.	
	Anemia due to zidovudine in HIV infected patients	100 Units/kg intravenously or subcutaneously three times weekly	Varies depending on indication and frequency of administration
	Anemia due to chemotherapy	40,000 Units subcutaneously weekly or 150 Units/kg subcutaneously three times weekly (adults) until completion of a chemotherapy course; 600 Units/kg intravenously weekly (children 5 years of age or older) until completion of a chemotherapy course	Varies depending on indication and frequency of administration
	Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery	300 Units/kg per day subcutaneously daily for 15 days total (administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery) or 600 Units/kg subcutaneously weekly in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery	Varies depending on indication and frequency of administration

Dosage Forms

- epoetin alfa (Epogen®): Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, and 10,000 units/mL; Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL.
- epoetin alfa (Procrit®): Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, and 40,000 units/mL; Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL.
- epoetin alfa-epbx (Retacrit®): Single-dose vial: 2,000 units/mL, 3,000 units/mL, 4,000 units/mL, 10,000 units/mL, 40,000 units/mL; Multiple-dose vial containing benzyl alcohol: 20,000 units/2 mL and 20,000 units/mL.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Anemia due to chronic kidney disease (must meet all):

1. Diagnosis of anemia of chronic kidney disease (dialysis and non-dialysis members);
2. Prescribed by or in consultation with a hematologist or nephrologist;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or serum transferrin saturation of 20% or greater;
4. Pre-treatment hemoglobin level less than 10 g/dL;
5. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Anemia due to zidovudine in HIV-infected patients (must meet all):
1. Diagnosis of zidovudine-induced anemia;
2. Prescribed by or in consultation with a hematologist or human immunodeficiency virus specialist;
3. Member is human immunodeficiency virus-positive;
4. Dose of zidovudine is 4,200 mg/week or less;
5. Current (within the last 3 months) endogenous serum erythropoietin levels is 500 mU/mL or less;
6. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or serum transferrin saturation of 20% or greater;
7. Pre-treatment hemoglobin level less than 10 g/dL;
8. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

C. Anemia due to chemotherapy in patients with cancer (must meet all):
1. Diagnosis of anemia due to chemotherapy;
2. Diagnosis of moderate to severe chronic kidney disease;
3. Member is undergoing palliative treatment and refused blood transfusions;
4. Member has a minimum of two additional months of planned chemotherapy;
5. Prescribed by or in consultation with a hematologist or oncologist;
6. Age 5 years of age or older;
7. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater;
8. Pre-treatment hemoglobin level less than 10 g/dL;
9. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery (must meet all):
1. Member is at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery;
2. Perioperative hemoglobin is greater than 10 but not greater than 13 g/dL;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater;

4. Member is unwilling or unable to donate autologous blood pre-operatively;
5. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 15 days (for 300 Units/kg daily) or 21 days (for 600 Units/kg in 4 doses)
Medicaid: 15 days (for 300 Units/kg daily) or 21 days (for 600 Units/kg in 4 doses)

E. Anemia Associated with myelodysplastic syndromes (off-label) (must meet all):
1. Diagnosis of anemia from myelodysplastic syndrome (MDS);
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age 18 years of age or older;
4. Current (within the last 3 months) endogenous serum erythropoietin (EPO) is 500 mU/mL or less;
5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater;
6. Pre-treatment hemoglobin level less than 10 g/dL;
7. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

F. Myelofibrosis-associated anemia (off-label) (must meet all):
1. Diagnosis of anemia associated with myelofibrosis;
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age 18 years of age or older;
4. Current (within the last 3 months) endogenous serum erythropoietin (EPO) is less than 500 mU/ml;
5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater;
6. If Epogen® or Procrit® is requested, failure of Retacrit® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Anemia due to chronic kidney disease (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Anemia due to zidovudine in HIV-infected patients (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;

2. Current hemoglobin level is 12 g/dL or less;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

C. Anemia due to chemotherapy in patients with cancer (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Continuation of ESA therapy is concurrent with myelosuppressive chemotherapy;
3. If member has received greater than or equal to 8 weeks of ESA therapy, member meets both of the following (a and b):
   a. Documented evidence of response to therapy as evidenced by rise in hemoglobin levels of 1g/dL or greater;
   b. No RBC transfusions are required;
4. Current hemoglobin less than 10 g/dL;
5. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater.

Approval Duration
Commercial: Until the completion of chemotherapy course or 6 months, whichever is longer
Medicaid: Until the completion of chemotherapy course or 6 months, whichever is longer

D. Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular Surgery
1. Re-authorization is not permitted.

Approval Duration
Not Applicable

E. Anemia Associated with myelodysplastic syndrome (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Current hemoglobin is 12 g/dL or less;
4. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

F. Myelofibrosis-associated anemia (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Adequate iron stores as indicated by current (within the last 3 months) serum ferritin level of 100 mcg/L or greater or serum transferrin saturation of 20% or greater.

Approval Duration
Commercial: 6 months

Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CKD: Chronic Kidney Disease
ESA: Erythropoiesis-Stimulating Agent
FDA: Food and Drug Administration
HIV: Human Immunodeficiency Virus
IV: Intravenous
RBC: Red Blood Cell

APPENDIX B: Therapeutic Alternatives

Not applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Uncontrolled hypertension;
  - Pure red cell aplasia (PRCA) that begins after treatment with erythropoietin protein drugs
  - Allergic reactions;
  - Use of the multiple-dose vials containing benzyl alcohol in neonates, infants, pregnant women, and lactating women.

- Boxed Warning(s):
  - Erythropoiesis-stimulating agents increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.

APPENDIX D: General Information

- Using ESAs to target a hemoglobin level of greater than 11 g/dL increase the risk of serious adverse cardiovascular reactions and have not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke.
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer.
- Control hypertension prior to initiating and during treatment with ESAs.
- Epoetin alfa products increase the risk for seizures in patients with CKD. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms.
- If severe anemia and low reticulocyte count develop during ESAs treatment, withhold ESAs, and evaluate for pure red cell aplasia.
- Serious Allergic Reactions: Discontinue ESAs and manage reactions.
- Severe Cutaneous Reactions: Discontinue ESAs.

References

1. Epogen® Prescribing Information. Thousand Oaks, CA: Amgen Inc.; July 2018. Available at http://www.epogen.com/. Accessed July 14, 2021.
2. Procrit® Prescribing Information. Thousand Oaks, CA: Amgen Inc.; July 2018. Available at http://www.procrit.com/. Accessed July 14, 2021.
3. Rizzo JD, Brouwers M, Hurley P, et al (2010). American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. Blood 2010; 116(20):4045-4059. Accessed January 4, 2018. Available at https://doi.org/10.1182/blood-2010-08-300541. Accessed July 14, 2021.

4. Mancino P, Falasca K, Ucciferri C, Pizzigallo E, Vecchiet J. Use of Hematopoietic Growth Factor in the Management of Hematological Side Effects Associated to Antiviral Treatment for Hcv Hepatitis. Mediterranean Journal of Hematology and Infectious Diseases. 2010;2(1):e2010003. doi:10.4084/MJHID.2010.003. Available at https://pubmed.ncbi.nlm.nih.gov/21415945/. Accessed July 14, 2021.
5. Afdhal NH, Dieterich DT, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology. 2004 May;126(5):1302-11. Available at https://pubmed.ncbi.nlm.nih.gov/15131791/. Accessed July 14, 2021.
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11. Epoetin alfa. In: Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed July 14, 2021.
12. Hematopoietic Growth Factors (Version 4.2021). In National Comprehensive Cancer Network Guidelines. Available at https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed July 14, 2021

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy Reviewed. 1. Formatting updated. 2. References updated. 3. Clinical policy title updated. 4. Drug(s) Applied updated. 5. Line of Business updated. 6. Continued therapy criteria updated.	06/30/2020	9/14/2020
Policy was reviewed: 1. Dosing Information table was updated to remove off-label indications “anemia associated with MDS” and “anemia associated with myelofibrosis” in addition to their respective dosing regimens and maximum doses. 2. Dosage Forms was updated from table format to bullet-list format. 3. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy.	07/14/2021	09/14/2021

4. Initial Approval Criteria I.C.2 was updated to include “Diagnosis of moderate to severe chronic kidney disease”. 5. Initial Approval criteria I.C.3 was updated to include “Member is undergoing palliative treatment and refused blood transfusions”. 6. Initial Approval Criteria I.C.4 was updated to include “Member has a minimum of two additional months of planned chemotherapy”. 7. Initial Approval Criteria I.C Approval Durations for Commercial and Medicaid were updated from “until the completion of chemotherapy course or 6 months, whichever is long” to “6 months”. 8. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 9. Continued Therapy Approval Criteria II.B.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 10. Continued Therapy Approval Criteria II.C.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 11. Continued Therapy Approval Criteria II.E.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 12. Continued Therapy Approval Criteria II.F.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...".		

13. Appendix A was updated to remove abbreviation SC. 14. Appendix D was updated to include "Using ESAs to target a hemoglobin level of greater than 11 g/dL increase the risk of serious adverse…", "Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer…", "Control hypertension prior to initiating and during treatment with ESAs…", "Epoetin alfa products increase the risk for seizures in patients with CKD…", "If severe anemia and low reticulocyte count develop during ESAs treatment…", "Serious Allergic Reactions: Discontinue ESAs and manage reactions…", and "Severe Cutaneous Reactions: Discontinue ESAs…". 15. References were reviewed and updated.		