



Horizon BCBSNJ  
 Medical Necessity Guideline

<b>Section</b>	Drugs
<b>Policy Number</b>	
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9/26/08,  
5/12/09

**Subject:**

**BRAND NAME:** Epogen, Procrit (all injectable)  
**(Generic)** (epoetin alfa)

**IMPORTANT NOTE:**

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

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**BLACK BOX WARNINGS:**

**Renal failure:** Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in 2 clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

**Cancer:**

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of 12 g/dL or more.
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of less than 12 g/dL.
- To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.
- Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- Discontinue following the completion of a chemotherapy course.

**Perisurgery:** Epoetin alfa increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

Throughout this document Epogen and Procrit will be referred to as epoetin alfa.

### **FDA APPROVED INDICATIONS**<sup>1,2</sup>

#### ***Treatment of anemia of chronic renal failure (CRF) patients***

Epoetin alfa is indicated for the treatment of anemia associated with chronic renal failure (CRF), including patients on dialysis (ESRD) and patients not on dialysis. Epoetin alfa is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit less than 30%. Epoetin alfa is not intended for patients who require immediate correction of severe anemia. Epoetin alfa may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of epoetin alfa therapy, and must be closely monitored and controlled during therapy. Epoetin alfa should be administered under the guidance of a qualified physician.

#### ***Treatment of anemia related to Zidovudine therapy $\leq$ 4200mg/week in HIV-infected patients.***

Epoetin alfa is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. Epoetin alfa is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. Epoetin alfa is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

Epoetin alfa, at a dose of 100 U/kg three times weekly (TIW), is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum epoetin alfa level is  $\leq$ 500 mUnits/mL and when patients are receiving a dose of zidovudine  $\leq$ 4200 mg/week.

#### ***Treatment of anemia in cancer patients with non-myeloid malignancy on chemotherapy.***

Epoetin alfa is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Epoetin alfa is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of two months. Epoetin alfa is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

#### ***Reduction of allogenic blood transfusion in surgery patients***

Epoetin alfa is indicated for the treatment of anemic patients (hemoglobin  $>10$  g/dL to  $\leq$  13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions. Epoetin alfa is indicated for patients at a high risk for perioperative transfusions with significant, anticipated blood loss. Epoetin alfa is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of epoetin alfa has been studied only in patients who are receiving anticoagulant prophylaxis.

### **Orphan Drug Status and Approved Compindial Use:**<sup>7,8</sup>

- Anemia associated with myelodysplastic syndromes.
- Anemia associated with the treatment of ribavirin/interferon alfa-2b therapy for chronic hepatitis C.
- Anemia following allogenic bone marrow transplantation.
- Anemia associated with chronic disease excluding malignancy (e.g., rheumatoid arthritis, inflammatory bowel diseases, congestive heart failure, HIV-induced.)

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of epoetin alfa therapy, and must be closely monitored and controlled during therapy. Epoetin alfa should be administered under the guidance of a qualified physician.

**Medical Necessity Guideline:**

1. The following questionnaire may be used to determine medical necessity of Epoetin alfa prescriptions.

**CRITERIA FOR APPROVAL:**

1. Does the patient have a diagnosis of chronic kidney disease? [If the answer to this question is no, may skip to question 6]	Yes	No
2. Has the patient received epoetin within the previous month? No [If the answer to this question is no, may skip to question 4]		Yes
3. Does the patient have hemoglobin of < 12 g/dL or hematocrit of < 36%? [Skip to question 17]	Yes	No
4. Does the patient have a glomerular filtration rate (GFR) of less than 60 mL/min? [If the answer to this question is no, no further questions required]	Yes	No
5. Does the patient have the diagnosis of anemia (hematocrit < 33% or hemoglobin < 11 g/dL)? [Skip to question 12]	Yes	No
6. Is the patient having elective, noncardiac, nonvascular surgery with high risk for perioperative transfusions with significant anticipated blood loss? [If the answer to this question is no, then skip to question 8.]	Yes	No
7. Is the hemoglobin of the patient $\leq$ 13 g/dL? [Skip to question 12.]	Yes	No
8. Does the patient have one of the following diagnosis: -HIV-related anemia secondary to treatment with zidovudine (AZT) doses of > 4200 mg/week -myelodysplastic syndrome -chemotherapy induced anemia in members with non-myeloid malignancies -chronic hepatitis C infection receiving treatment with ribavirin -anemia following an allogeneic bone marrow transplant -anemia associated with chronic diseases excluding malignancy (e.g., rheumatoid arthritis, inflammatory bowel diseases, congestive heart failure, HIV-induced) [If the answer to this question is no, then no further questions required.]	Yes	No
9. Has the patient received epoetin within the previous month? [If the answer to this question is no, may skip to question 11.]	Yes	No
10. Does the patient have hemoglobin of < 12 g/dL or hematocrit of < 36%? [Skip to question 17]	Yes	No
11. Does the patient have a diagnosis of anemia (hematocrit <30% or hemoglobin < 10g/dL)? [If the answer to this question is no, no further questions required]	Yes	No
12. Upon initial evaluation, were the following evaluated: -other causes of anemia (e.g., iron deficiency, folate deficiency, hemolysis, or gastrointestinal bleeding) eliminated -blood pressure	Yes	No
13. Is the serum ferritin concentration of the patient > 100 mg/L and is the transferrin saturation		

of the patient > 20%? [If the answer to this question is yes, may skip to question 15]	Yes	No
14. Is the patient currently taking, or will the patient be receiving iron supplementation?	Yes	No
15. Will the patient's blood pressure be monitored throughout therapy, and the hemoglobin level monitored every 2 weeks, <b>when initiating therapy or for dose changes</b> , at regular intervals (e.g., at least quarterly) <b>when the dose is stabilized</b> ?	Yes	No
16. Will the physician consider the following: -For renal failure patients: individualize dosing to achieve and maintain target Hgb levels under 12 g/dL -For cancer patients: use lowest dose needed to avoid red blood cell transfusions, use only for anemia due to concomitant myelosuppressive chemotherapy, discontinue following the completion of chemotherapy course -Perisurgery: consider deep venous thrombosis prophylaxis [Skip to question 18.]	Yes	No
17. Has the patient been on therapy for at least 12 weeks? [If the answer to this question is no, then skip to question 19]	Yes	No
18. Has a clinical response to therapy been achieved (e.g., increase in Hgb of > 1 g/dL, decrease in duration or number of transfusions)?	Yes	No
19. Is the request for more than the following dispensing limits? -Epogen/Procrit (40,000 unit vial) in a dose more than 60,000 units per week -Epogen/Procrit (except 40,000 unit vial) more than 3 injections per week	Yes	No

Guidelines for Approval							
Duration of Approval				8 weeks			
<b>SET 1-CKD-No Fe</b>		<b>SET 2 – Surgery – No Fe</b>		<b>SET 3 – Others – No Fe</b>		<b>SET 4 – CKD – Fe</b>	
<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>
1	2	6	1	8	1	1	2
4	19	7	19	11	6	4	13
5		12		12	9	5	19
12		13		13	19	12	
13		15		15		14	
15		16		16		15	
16						16	
<b>SET 5 – Surgery - Fe</b>		<b>SET 6 – Others - Fe</b>		<b>SET 7 -CKD – Renewal, on therapy ≥12 weeks</b>		<b>SET 8 – CKD – Renewal on therapy &lt;12 weeks</b>	
<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>
6	1	8	1	1	19	1	17
7	13	11	6	2		2	19
12	19	12	9	3		3	
14		14	13	17			
15		15	19	18			
16		16					
<b>SET 9 - Others – Renewal, on therapy ≥12 weeks</b>		<b>SET 10 – Others – Renewal, on therapy &lt;12 weeks</b>					
<b>YES to question(s)</b>	<b>NO to question(s)</b>	<b>YES to question(s)</b>	<b>NO to question(s)</b>				
8	1	8	1				

9	6	9	6
10	19	10	17
17			19
18			

**Horizon BCBSNJ Pharmacy Guideline Development Process:** This Horizon BCBSNJ Pharmacy Guideline (the "Pharmacy Guideline") has been developed by Horizon BCBSNJ's Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

**Rationale**

The intent of the criteria is to ensure that patients follow selection elements established by Horizon BCBS New Jersey's medical policies.

**ADDITIONAL INFORMATION:**

***Dose: General guide to therapy in CRF patients:***

Prior to initiating therapy a patient's iron stores should be evaluated, including serum transferrin and serum ferritin. Transferrin saturation should be at least 20% and serum ferritin should be at least 100 ng/mL. Prior to and during therapy, patient's iron stores should be monitored, including transferrin saturation and serum ferritin. Hematocrit should be determined twice weekly after treatment initiation or dosage adjustment until it has stabilized; then monitor at regular intervals. Dosage adjustment should not be made more frequently than once a month unless clinically indicated. After any dosage adjustment, determine the hematocrit twice weekly for at least 2 to 6 weeks.

***Initial dose:*** 50-100 U/kg three times weekly IV or SC

***Reduce dose if:*** 1) Hematocrit approaches 36% or  
2) Hematocrit increases > 4 points in any two week period.

***Increase dose if:*** 1) Hematocrit does not increase by five to six points after eight weeks of therapy, and hematocrit is below suggested target range.

***Maintenance dose:*** Individualize

***Zidovudine-treated HIV-infected patients:***

Prior to therapy initiation, determine the endogenous serum epoetin alfa level prior to transfusion. Available evidence suggests that patients receiving zidovudine with endogenous serum epoetin alfa levels > 500 mU/ml are unlikely to respond to therapy. Monitor hematocrit weekly during the dosage adjustment phase of therapy.

**Initial dose:** 100U/kg three times weekly IV or SC for eight weeks if  
1) Serum epoetin alfa levels are  $\leq$  500 mU/mL  
2) Patient is receiving a dose of zidovudine  $\leq$  4200 mg/week

After 8 weeks, if response is not satisfactory in reducing transfusion requirements or increasing hematocrit then the dose may be increased by 50 to 100 U/kg three times weekly. Evaluate response every four to eight weeks thereafter and adjust the dose accordingly by 50 to 100 U/kg increments three times weekly.

(If patient has not responded satisfactorily to a 300 U/kg dose three times weekly, it is unlikely that they will respond to higher doses).

**Maintenance dose:** When the desired response is achieved, titrate the dose to maintain the response based on factors such as variations in zidovudine therapy and the presence of infections or inflammation.

#### **Cancer patients on chemotherapy:**

**Initial dose:** 150 U/kg SC three times weekly.

**Dosage Adjustment:** If response is not satisfactory in terms of reducing transfusion requirement or increasing hematocrit after eight weeks of therapy, the dose may be increased up to 300 U/kg three times weekly.

If hematocrit exceeds 40%, hold the dose until hematocrit falls to 36%. Reduce dose by 25% when treatment is resumed and titrate to maintain desired hematocrit. If initial dose produces a very rapid hematocrit response, reduce the dose.

#### **Surgery:**

Prior to administration obtain an established hemoglobin of > 10 to  $\leq$ 13 g/dl.

**Dosage:** 300 U/kg/ SC daily for the 10 days prior to surgery, the day of surgery, and four days after surgery.

**or**

600 U/kg SC once weekly for three weeks prior to surgery and a fourth dose the day of surgery

Some studies have been published where Epoetin beta was used for treatment, particularly in myeloid malignancies. Since the interchangeability of Epoetin alpha and beta has not been established, and the beta product is not available in the United States, those studies have not been considered.

#### **CONTRAINDICATIONS:**

- Do not use if patient has uncontrolled hypertension.
- Do not use in patients with known hypersensitivity to mammalian cell-derived products.

- Do not use in patients with a known hypersensitivity to albumin (human)

## **WARNINGS:**

### **Pediatric Use**

The multidose preserved formulation of epoetin alfa contains benzyl alcohol which has been reported to be associated with an increased incidence of neurological and other complications in premature infants. Safety and effectiveness have not been established in pediatric patients.

### **Thrombotic Events and Increased Mortality**

In patients at risk for thrombosis, the benefits of epoetin alfa therapy should be weighed against the potential for increased risks associated with therapy.

In a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease, patients were assigned to epoetin alfa treatment groups with differing hematocrit goals ( $42 \pm 3\%$  vs.  $30 \pm 3\%$ ). The results showed an increase in mortality, nonfatal myocardial infarctions, vascular access thromboses and all other thrombotic events in the treatment group with a goal hematocrit of  $42 \pm 3\%$ .

Increased mortality was also observed in a randomized placebo-controlled study of epoetin alfa in patients who did not have chronic renal failure and who were undergoing coronary artery bypass surgery (7/126 deaths in treatment group vs. 0/54 deaths in placebo group).

### **Chronic Renal Failure Patients (CRF)**

Special care should be taken to closely monitor and control blood pressure in patients treated with epoetin alfa. Patients with uncontrolled hypertension should not be treated with epoetin alfa; blood pressure should be controlled adequately before initiation of therapy. In the early phase of treatment, when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases, in anti-hypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with chronic renal failure treated with epoetin alfa.

It is recommended that the dose of epoetin alfa be decreased if the hematocrit increase exceeds 4 points in any 2-week period. A rapid rise in hematocrit has been associated with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or chronic heart failure, hematocrit should not exceed 36%.

There is an increased risk of seizures associated with epoetin alfa therapy in CRF patients on dialysis during the first 90 days of therapy. Blood pressure and presence of premonitory neurologic symptoms should be followed closely. Patients should be cautioned to avoid potentially hazardous activity such as driving or operating heavy machinery during this period.

During hemodialysis, patients treated with epoetin alfa may require increased anticoagulation with heparin to prevent clotting of the dialyzer unit. Other thrombotic events have occurred in clinical trials at an annualized rate of less than 0.04 events per patient per year of epoetin alfa. Patients with pre-existing cardiovascular disease should be monitored closely.

## **PRECAUTIONS:**

The safety and efficacy of epoetin alfa therapy have not been established in patients with known history of a seizure disorder or underlying hematologic disease (ie, sickle cell anemia or hypercoagulable disorders).

Exacerbation of porphyria has rarely been observed in patients with CRF treated with epoetin alfa. Epoetin alfa should be used with caution in patients who have known porphyria.

*Delayed or Diminished Response:* If the patient fails to respond or to maintain a response to doses within the recommended dosing range, then the following etiologies should be considered and evaluated:

- Iron deficiency: Virtually all patients will eventually require supplemental iron therapy
- Underlying infectious, inflammatory or malignant process

- Occult blood loss
- Underlying hematologic disease (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders)
- Vitamin deficiencies: Folic acid or vitamin B12
- Hemolysis
- Aluminum toxicity
- Osteitis fibrosa cystica
- Pure Red Cell Aplasia (PRCA): In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to recombinant erythropoietins.

Prior to and during epoetin alfa therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20% and ferritin should be at least 100ng/ml. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by epoetin alpha.

## **REFERENCES**

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