



Horizon BCBSNJ  
Medical Necessity Guideline

<b>Section</b>	Drugs
<b>Policy Number</b>	
<b>Effective Date</b>	6/25/04
<b>Review Date</b>	6/2/06, 9/25/06, 9/26/08

**Subject:**

**BRAND NAME:**                    **Aranesp (all injectable)**  
**(Generic)**                           **(darbepoetin 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.*

**Horizon BCBSNJ pharmacy guidelines do not constitute medical advice, authorization, certification, approval, explanation of benefits, offer of coverage, contract or guarantee of payment.**

**BLACK BOX WARNINGS:**

**Increased mortality, serious cardiovascular and thromboembolic events, and tumor progression:**

**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 and 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

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

Aranesp is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

### **Orphan Drug Status and Approved Compendial Use**

Anemia associated with myelodysplastic syndromes.

Anemia associated with the treatment of ribavirin/interferon alfa-2b therapy for chronic hepatitis C.

Anemia following allogeneic bone marrow transplantation.

Anemia associated with chronic disease excluding malignancy (e.g., rheumatoid arthritis, inflammatory bowel diseases, congestive heart failure, HIV-induced.)

### **Medical Necessity Guideline:**

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

#### **CRITERIA FOR APPROVAL:**

- |  |     |    |
|--|-----|----|
| 1. Does the patient have a diagnosis of chronic kidney disease?<br>[If the answer to this question is no, may skip to question 6]  | Yes | No |
| 2. Has the patient received darbepoetin alfa within the previous month?<br>[If the answer to this question is no, may skip to question 4]  | Yes | No |
| 3. Does the patient have a hemoglobin of 11-12 g/dL or hematocrit of 33-36%?<br>[Skip to question 15]  | Yes | No |
| 4. Does the patient have a glomerular filtration rate (GFR) of less than 60 mL/min?<br>[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)?<br>[Skip to question 10]  | Yes | No |
| 6. Does the patient have one of the following diagnosis:<br>-myelodysplastic syndrome<br>-- chemotherapy induced anemia in members with non-myeloid malignancies<br>-chronic hepatitis C infection receiving treatment with ribavirin<br>-anemia following an allogeneic bone marrow transplant<br>-anemia associated with chronic diseases excluding malignancy (e.g., rheumatoid arthritis, inflammatory bowel diseases, congestive heart failure, HIV-induced)<br>[If the answer to this question is no, then no further questions required.] | Yes | No |
| 7. Has the patient received darbepoetin alfa within the previous month?<br>[If the answer to this question is no, may skip to question 9.]   | Yes | No |
| 8. Does the patient have a hematocrit of 30-36% or hemoglobin of 10-12 g/dL?<br>[Skip to question 15]  | Yes | No |
| 9. Does the patient have a diagnosis of anemia (hematocrit <30% or hemoglobin < 10g/dL)?<br>[If the answer to this question is no, no further questions required]  | Yes | No |
| 10. Upon initial evaluation, were the following evaluated:<br>-other causes of anemia (e.g., iron deficiency, folate deficiency, hemolysis, or gastrointestinal bleeding) eliminated<br>-blood pressure  | Yes | No |

11. 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 13]	Yes	No
12. Is the patient currently taking, or will the patient be receiving iron supplementation?	Yes	No
13. 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
14. Will the physician considered 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 [Skip to question 16.]	Yes	No
15. If the patient has had 12 weeks of therapy, was response achieved (e.g., increase in Hgb of > 1 g/dL, decrease in duration or number of transfusions)?	Yes	No
16. Will the patient require more than one injection of Aranesp every 14 days?	Yes	No

Guidelines for Approval							
Duration of Approval				3 month			
SET 1 – CKD – w/Fe		SET 2 – CKD – No Fe		SET 3 – CKD Renewal		SET 4 – Other Dx – w/Fe	
YES to question(s)	NO to question(s)	YES to question(s)	NO to question(s)	YES to question(s)	NO to question(s)	YES to question(s)	NO to question(s)
1	2	1	2	1	16	6	1
4	11	4	16	2		9	7
5	16	5		3		10	11
10		10		15		12	16
12		11				13	
13		13				14	
14		14					
SET 5 – Other Dx – No Fe		SET 6– Other DX Renewal					
YES to question(s)	NO to question(s)	YES to question(s)	NO to question(s)				
6	1	6	1				
9	7	7	16				
10	16	15					
11		8					
13							
14							

**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 and Administration:**

**IMPORTANT: Aranesp dosing regimens are different for each of the indications. Due to the longer serum half-life, Aranesp should be administered less frequently than epoetin alfa. For example, where epoetin alfa is administered, three times a week, Aranesp should be administered weekly. Aranesp should be administered under the supervision of a healthcare professional.**

#### **Chronic Renal Failure:**

Aranesp is administered either intravenously (IV) or subcutaneously (SC) as a single weekly injection. The dose should be started and slowly adjusted based on hemoglobin levels. If a patient fails to respond or maintain response, other etiologies should be considered and evaluated. When Aranesp therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp with a rapid increase in hemoglobin, more than 1.0 g/dL in any 2-week period, the dose of Aranesp should be reduced because of the association of excessive rate of rise of hemoglobin with adverse events.

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dL.

The recommended starting dose of Aranesp for the correction of anemia in CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of Aranesp administered once every two weeks.

#### **Conversion from Epoetin Alfa in Chronic Renal Failure:**

When converting from epoetin alfa to darbepoetin alfa, the starting weekly dose of darbepoetin should be estimated on the basis of the weekly total epoetin alfa dose at the time of substitution. Due to patient variability, doses should then be titrated to maintain the target hemoglobin level. Aranesp, which has a longer half-life, is administered less frequently than epoetin alfa. Aranesp should be administered once a week in patients who have been receiving epoetin alfa two to three times per week. When a patient is receiving epoetin alfa once a week, Aranesp should be administered every two weeks. The route of administration, either IV or SC, should be consistent.

#### **Dose Adjustments in Chronic Renal Failure:**

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25 percent. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25 percent below the previous dose. If the hemoglobin increases by more than 1.0 gm/dL in a 2-week period or if the hemoglobin exceeds 12 g/dL, the dose should be reduced by approximately 25%. If the dose exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25 percent below the previous dose.

#### **Cancer Patients Receiving Chemotherapy:**

The recommended starting dose for Aranesp is 2.25 mcg/kg administered as a weekly subcutaneous injection. The dose should be adjusted for each patient to achieve and maintain the target hemoglobin. If there is less than 1.0 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp should be increased up to 4.5 mcg/kg. If hemoglobin increased by more than 1.0 g/dL in a 2-week period or if the hemoglobin exceeds 12 g/dL, the dose should be reduced by 25 percent. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25 percent below the previous dose.

**DO NOT SHAKE** Aranesp. Vigorous shaking may denature Aranesp, rendering it biologically inactive.

#### **DO NOT POOL UNUSED PORTIONS**

#### **CONTRAINDICATIONS/WARNINGS/PRECAUTIONS:**

##### **Contraindications:**

- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients

##### **Warnings:**

- Darbepoetin alfa and other erythropoietic therapies may increase the risk of cardiovascular events, including death. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 12 g/dL.
- Patients with uncontrolled hypertension should not be treated with darbepoetin alfa. The blood pressure should be controlled adequately prior to the initiation of therapy. Also, blood pressure may rise during the treatment of anemia with darbepoetin alfa. In clinical trials, approximately 40% of patients required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with chronic renal failure treated with Aranesp. Therefore, special care should be taken to closely monitor and control blood pressure in patients being treated with darbepoetin alfa. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp should be reduced or withheld.
- Seizures have occurred in patients with chronic renal failure participating in clinical trials of Aranesp and epoetin alfa.
- An increased incidence of thrombotic events has been observed in patients treated with erythropoietic agents. In patients with cancer who received Aranesp, pulmonary emboli, thrombophlebitis and thrombosis occurred more frequently than in placebo controls.
- Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin has been observed in patients treated with recombinant erythropoietins. This has been reported predominantly in patients with chronic renal failure. Any patient with loss of response to Aranesp should be evaluated for the etiology of loss of effect. Aranesp should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to Aranesp, native erythropoietin, and any other recombinant erythropoietin administered to the patient. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, Aranesp should not be administered.

- Darbepoetin alfa is supplied in two formulations, one containing polysorbate 80 and another containing human albumin, a derivative of human blood. With precautions taken in the manufacturing process, formulations with albumin carry an extremely remote risk for transmission of viral disease. A theoretical risk of transmission of Creutzfeldt-Jakob disease also is considered extremely remote. No cases of transmission of viral diseases or Creutzfeldt-Jakob disease have ever been identified in the albumin formulation.

**Precautions:**

- The safety and efficacy of darbepoetin alfa therapy have not been established in patients with underlying hematologic diseases (eg, hemolytic anemia, sickle cell anemia, thalassemia and porphyria).
  - A lack of response or failure to maintain a hemoglobin response with Aranesp does within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B-12 should be excluded or corrected. Intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity and bone marrow fibrosis may compromise an erythropoietic response.
  - There have been rare reports of potentially serious allergic reactions including skin rash and urticaria associated with Aranesp. Symptoms have recurred with rechallenge. If a serious allergic or anaphylactic reaction occurs, Aranesp should be immediately and permanently discontinued and appropriate therapy should be administered.
  - Aranesp is a growth factor that primarily stimulates red blood cell production. The possibility that Aranesp can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated.
  - The safety and efficacy of darbepoetin alfa in pediatric patients have not been established

**REFERENCES:**

1. Aranesp Product Information. Amgen Inc. December 2005.
2. American Hospital Formulary Service. American Society of Health-System Pharmacists. 2006.
3. USPDI. Thomson MICROMEDEX. 2006.

*Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.*

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