MEDICAL MUTUAL®

Drug Policy

Policy:	**201312**	**Initial Effective Date: 04/01/2013**
Code(s):	**HCPCS J0881**	**Annual Review Date: 09/20/2018**
SUBJECT:	**Erythropoiesis Stimulating Agents** **- Darbepoetin Alfa (Aranesp®)**	**Last Revised Date: 12/28/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Aranesp is an erythoid stimulating agent (ESA) that is approved for the following indications:[1]

1) Treatment of anemia with chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.
2) Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Aranesp is available as single-dose vials and as single-dose prefilled syringes (SingleJect®) in various strengths and package sizes.

POLICY STATEMENT

This policy involves the use of darbepoetin alfa. Prior authorization is recommended for pharmacy and medical benefit coverage of darbepoetin alfa. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing (medical benefit requests only), Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions that are administered by a healthcare professional. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with darbepoetin alfa as well as the monitoring required for AEs and long-term efficacy, initial approval requires darbepoetin alfa be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

The site of care medical necessity criteria applies to initial therapy and reauthorizations under the medical benefit.

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RECOMMENDED AUTHORIZATION CRITERIA
Coverage of darbepoetin alfa is recommended in those who meet the following criteria:

1. **Anemia in Patients with Chronic Kidney Disease (CKD) who are on Dialysis. – No prior approval needed for this indication.**

Criteria. *The patient must meet the following criteria (A, B, C, D, and E)*:
A. For initial therapy, hemoglobin (Hb) is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children; OR
For patients currently receiving Aranesp, epoetin alfa, or Mircera (methoxy polyethylene glycol-epoetin beta injection for intravenous or subcutaneous use), Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children; AND
B. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%).
C. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate; AND
D. The dose of darbepoetin is individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL; AND
E. Site of care medical necessity is met*.

Dosing in Patients with CKD who are on Dialysis *(medical benefit only)*. *Dosing must meet the following (A OR B):*
A) For adults or children, initiate therapy at 0.45 mcg/kg subcutaneously (SC) or intravenously (IV) as a single injection once weekly; OR
B) For adults, initiate therapy at 0.75 mcg/kg SC or IV once every 2 weeks.

Initial Approval/Extended Approval.
a) *Initial Approval*. Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.
b) *Extended Approval*. Extended approval is at 6-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol for dose reduction and withholding doses if subsequest Hb values exceed 12g/dL.

Duration of Therapy in Patients with CKD who are on Dialysis. Indefinite as long as the patient has CKD and is receiving dialysis.

Labs/Diagnostics. *Patient must meet the following criteria (a AND b)*:
a) Monitor Hb at therapy initiation and at 6-month intervals; AND

b) Iron stores (for example, serum iron, total iron binding capacity, serum ferritin, percent transferrin saturation [TSAT], bone marrow biopsy) must be evaluated at therapy initiation and at 6-month intervals, unless the patient is currently receiving iron therapy.

2. Anemia in Patients with Chronic Kidney Disease (CKD) who are not on Dialysis.

Criteria. *The patient must meet the following criteria (A, B, C, D and E)*:

A. For initial therapy Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children; OR
For patients currently receiving Aranesp or epoetin alfa, Hb is ≤ 11.5 g/dL for adults and ≤ 12.0 g/dL for children OR for patients currently receiving Mircera, Hb is ≤ 11.5 g/dL for adults; AND
B. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%).
C. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate; AND
D. The dose of darbepoetin is individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL; AND
E. Site of care medical necessity is met*.

Dosing in Patients with CKD who are not on Dialysis *(medical benefit only)*. *Dosing must meet the following (A or B):*

A) For adults, initiate therapy at 0.45 mcg/kg subcutaneously (SC) or intravenously (IV) once every 4 weeks; OR
B) For children, the starting dose is 0.45 mcg/kg body weight given as a single SC or IV injection once weekly OR 0.75 mcg/kg SC or IV once every 2 weeks.

Note: If Hb exceeds 11.5 g/dL for adults or 12.0 g/dL in children, reduce or interrupt the Aranesp dose, and use the lowest dose sufficient to reduce the need for RBC transfusions. Refer to the prescribing information regarding titration of Aranesp.[1]

Initial Approval/Extended Approval.

a) *Initial Approval*. Initial approval is for 6 months if Hb is < 10.0 g/dL for adults and ≤ 11.0 g/dL for children.
b) *Extended Approval*. Extended approval is at 6-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. For patients not responding discontinue Aranesp and evaluate and treat for other causes of anemia. If the Hb is > 12g/dL but the patient has had a previous beneficial response to therapy, the provider must have a protocol for dose reduction and withholding doses if subsequest Hb values exceed 12g/dL.

Duration of Therapy in Patients with CKD who are on Dialysis. Indefinite as long as the patient has CKD.

Labs/Diagnostics. *Patient must meet the following criteria (a AND b)*:

a) Monitor Hb at therapy initiation and at 6-month intervals; AND
b) Iron stores (for example, serum iron, total iron binding capacity, serum ferritin, percent transferrin saturation [TSAT], bone marrow biopsy) must be evaluated at therapy initiation and at 6-month intervals, unless the patient is currently receiving iron therapy.

3. Anemia in Patients with Cancer due to Cancer Chemotherapy.

Criteria. *The patient must meet the following criteria (A, B, C, D and E)*:

A. Hb is < 10.0 g/dL for initial therapy; OR
Hb is ≤ 12.0 g/dL for patients currently receiving Aranesp or epoetin alfa; AND
B. The patient is currently receiving myelosuppressive chemotherapy; AND
C. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum tranferrin saturation is < 20%).
D. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate; AND
E. Site of care medical necessity is met*.

Dosing in Anemia due to Cancer Chemotherapy *(medical benefit only)*. *Dosing for adults must meet ONE of the following (A, B, C, D, OR E)*:

A) 2.25 mcg/kg once weekly by SC injection (increase up to 4.5 mcg/kg weekly SC) until completion of a chemotherapy course[1]; OR
B) 500 mcg once every 3 weeks by SC injection until completion of a chemotherapy course[1]; OR
C) 100 mcg fixed dose once every week by SC injection (increase up to 150 to 200 mcg fixed dose once every week by SC injection) until completion of a chemotherapy course[5]; OR
D) 200 mcg fixed dose once every 2 weeks by SC injection (increase up to 300 mcg fixed dose once every 2 weeks by SC injection) until completion of a chemotherapy course[5]; OR
E) 300 mcg fixed dose once every 3 weeks by SC injection (increase up to 500 mcg fixed dose once every 3 weeks by SC injection) until completion of a chemotherapy course[5].

Initial Approval/Extended Approval.

a) *Initial Approval*. Initial approval is for 4 months if Hb is < 10 g/dL.
b) *Extended Approval*. Approval can be given at 4-month intervals if the Hb is ≤ 12.0 g/dL and the patient responds to therapy. Response is defined as Hb has increased, Hb has stayed the same and not decreased further, RBC transfusions are not required, and/or the number of RBC transfusions has decreased. If the patient does not have a response, discontinue Aranesp. Discontinue Aranesp following completion of a cancer chemotherapy course.

Duration of Therapy in Anemia due to Cancer Chemotherapy. Indefinite as long as the patient is receiving myelosuppressive chemotherapy.

Labs/Diagnostics. Patient must meet the following criteria (a AND b):

a) Monitor Hb at therapy initiation and at 4-month intervals; AND
b) Iron stores (for example, serum iron, total iron binding capacity, serum ferritin, TSAT, bone marrow biopsy) must be evaluated at therapy initiation and at 4-month intervals, unless the patient is currently receiving iron therapy.

Other Uses with Supportive Evidence

4. Anemia Associated with Myelodysplastic Syndrome (MDS).

Criteria. *The patient must meet the following criteria (A, B, C, D, E and F)*:
A. Patient is ≥ 18 years of age; AND
B. Hb is ≤ 10 g/dL for initial therapy; OR
serum erythropoietin level is ≤ 500 mU/mL for initial therapy; OR
Hb is ≤ 12.0 g/dL for patients currently receiving Aranesp or epoetin alfa; AND
C. Aranesp is prescribed by, or in consultation with, a hematologist or oncologist; AND
D. The patient is currently receiving iron therapy or iron stores are adequate (e.g., Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum tranferrin saturation is < 20%).
E. Evaluation for other causes of anemia, including nutritional causes, has been performed and condition treated as appropriate; AND
F. Site of care medical necessity is met*.

Dosing in MDS *(medical benefit only)*. *Dosing must meet ONE of the following (A OR B)*:
A) 150 to 300 mcg SC once every other week[7]; OR
B) 500 mcg SC once every other week or once every 3 weeks.[7,11,15]

Initial Approval/Extended Approval.
a) *Initial Approval*. Initial approval is for 6 months if Hb is ≤ 10 g/dL OR the serum erythropoietin level is ≤ 500 mU/mL.
b) *Extended Approval*. Approve at additional 6-month intervals if a response is achieved (increase in Hb or a decrease in transfusions) and Hb is ≤ 12.0 g/dL. For patients not responding, despite dose titrations and/or concomitant use of granulocyte colony stimulating factor (G-CSF) (e.g., Neupogen® [filgrastim injection]) during the first 6 months, discontinue Aranesp and evaluate and treat for other causes of anemia.

Duration of therapy in MDS. Indefinite as long as the patient has MDS.

Labs/Diagnostics. *Patient must meet the following criteria (A AND B)*:
a) Monitor Hb or serum erythropoietin levels at therapy initiation and monitor Hb at 6-month intervals; AND
b) Iron stores (for example, serum iron, total iron binding capacity, serum ferritin, TSAT, bone marrow biopsy) must be evaluated at therapy initiation and at 4-month intervals, unless the patient is currently receiving iron therapy.

Waste Management for All Indications.
Single-dose vials and syringes are available in many different strengths. The dose should be calculated and the number of vials/syringes needed assessed. Refer the corresponding package insert for more information: http://www.aranesp.com,

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Aranesp has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Anemia Associated with Cancer in Patients not Receiving Myelosuppressive Cancer Chemotherapy.** Aranesp is not indicated in patients with cancer who are not receiving cancer chemotherapy. The American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) guidelines for the use of Epogen/Procrit/Retacrit and Aranesp in adult patients with cancer recommend that ESAs not be used in treatment of anemia associated with malignancy in those who are not receiving concurrent myelosuppressive chemotherapy.

2. **Anemia Associated with Acute Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML), or other Myeloid Cancers.** Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.

3. **Anemia Associated with Radiotherapy in Cancer.** Aranesp is not indicated for use in cancer patients who are given only radiation therapy.

4. **To Enhance Athletic Performance.** Aranesp is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. **Anemia in Patients due to Acute Blood Loss.** Use of Aranesp is not appropriate in these types of situations.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Aranesp® injection for subcutaneous or intravenous use [prescribing information]. Thousand Oaks, CA: Amgen; April 2017.
2. Schaefer F, Hoppe B, Jungraithmayr T, et al. Safety and usage of darbepoetin alfa in children with chronic kidney disease: prospective registry study. *Pediatr Nephrol*. 2016;31:443-453.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Inter*. 2012;2(Suppl):279-335. Available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed on June 22, 2018.
4. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. *J Clin Oncol*. 2010;28(33):4996-5010.
5. The NCCN Cancer- and Chemotherapy-Induced Anemia Clinical Practice Guidelines in Oncology (Version 2.2018 – November 21, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on June 22, 2018.
6. Blumer J, Berg S, Adamson PC, et al. Pharmacokinetic evaluation of darbepoetin alfa for the treatment of pediatric patients with chemotherapy-induced anemia. *Pediatr Blood Cancer*. 2007;49:687-693.
7. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2018 – February 15, 2018). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on June 18, 2018.
8. Seastone DJ, Gerds AT. Darbepoetin alfa for anemia with myelodysplastic syndrome. *Expert Rev Hematol*. 2015;8(2):139-145.
9. Stasi R, Abruzzese E, Lanzetta G, et al. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-risk myelodysplastic syndromes. *Ann Oncol*. 2005;16:1921-1927.
10. Mannone L, Gardin C, Quarre MC, et al. High-dose darbepoetin alpha in the treatment of anemia of lower risk myelodysplastic syndrome: results of a phase II study. *Br J Haematol*. 2006;133(5):513-519.
11. Kelaidi C, Beyne-Rauzy O, Braun T, et al. High response rate and improved exercise capacity and quality of life with a new regimen of darbepoetin alfa with or without filgrastim in lower-risk myelodysplastic syndromes: a phase II study by the GFM. *Ann Hematol*. 2013;92:621-631.
12. Oliva EN, Nobile F, Alimena G, et al. Darbepoetin alfa for the treatment of anemia associated with myelodysplastic syndromes: efficacy and quality of life. *Leuk Lymphoma*. 2010;51(6):1007-1014.
13. Park S, Fenaux P, Greenberg P, et al. Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. *Br J Haematol*. 2016;174:730-747.
14. Warady BA, Barcia J, Benador N, et al. De novo weekly and biweekly darbepoetin alfa dosing in pediatric patients with chronic kidney disease. *Pediatr Nephrol*. 2018;33(1):125-137.
15. Platzbecker U, Symeonidis A, Oliva EN, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. *Leukemia*. 2017;31(9):1944-1950.

OTHER REFERENCES UTILIZED

- Solomon SD, Uno H, Lewis EF, et al, for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med*. 2010;363:1146-1155.

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FOR MEDICAL BENEFIT COVERAGE REQUESTS:

***MMO Site of Care Medical Necessity Criteria:**

- Medications in this policy will be administered in a place of service that is a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met[†]:

    1. Age is less than 18* years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Up to 1 dose of medication or re-initiation after at least 12 months; or
    7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

* Effective 01/01/2019, age criterion applies to 18 years of older. Age at original effective date (03/01/2016) was 21 years or older.
[†]This criterion does not apply to Medicare or Medicare Advantage members.

Prior approval is required for HCPCS Codes J0881

HCPCS Code(s):	
J0881	Injection, darbepoetin alfa, 1 microgram (non-ESRD use) 500

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