Medical Policy Bulletin
Title:
Erythropoiesis Stimulating Agents (ESAs)
Policy #:
MA08.011g

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

ANEMIA ASSOCIATED WITH CANCER AND RELATED ONCOLOGIC CONDITIONS

MEDICALLY NECESSARY CRITERIA FOR EPOETIN ALFA (EPOGEN®, PROCRIT®), DARBEPOETIN ALFA (ARANESP®) AND RELATED BIOSIMILARS (e.g., EPOETIN ALFA-EPBX [RETACRIT™])

Initiation Criteria for Erythropoiesis-Stimulating Agents (ESAs) Therapy for Cancer and Related Oncologic Conditions

Erythropoiesis-stimulating agents such as epoetin alfa (Epogen®, Procrit®), darbepoetin alfa (Aranesp®), or related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) are considered medically necessary and, therefore, covered when any of the following criteria are met:

- The individual has anemia secondary to a regimen of myelosuppressive anticancer chemotherapy for non-myeloid malignancies and has no other identifiable cause of anemia, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
    - The hemoglobin (Hb) level immediately prior to the first administration of ESA is less than 10 g/dL (or hematocrit [HCT] is less than 30 percent).
- The individual is undergoing palliative treatment.

Treatment of Chemotherapy-Induced Anemia

- As treatment of symptomatic chemotherapy-Induced anemia in individuals with cancer with any of the following:
    - Have moderate to severe chronic kidney disease
    - Are undergoing palliative treatment
    - Are receiving myelosuppressive chemotherapy and have no other identifiable cause of anemia
    - Refuse blood transfusions in select cases

National Comprehensive Cancer Network (NCCN) note: Erythropoiesis-stimulating agents are not recommended when myelosuppressive chemotherapy is given with curative intent (except for individuals who refuse blood

transfusions), for individuals with cancer who are not receiving therapy, or for individuals receiving non-myelosuppressive therapy.

Myelodysplastic Syndrome

For individuals with symptomatic anemia related to myelodysplastic syndrome, as treatment of lower risk† disease, when all of the following criteria are met:

- Individuals with one of the following:
  - As an alternative to lenalidomide, for individuals, with del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7) and serum erythropoietin ≤500 mU/mL
  - For individuals with no del(5q), with or without one other cytogenetic abnormalities ring sideroblasts <15 percent (or ring sideroblasts <5% with an SF3B1 mutation) with serum erythropoietin ≤500 mU/mL
    - As a single agent (NCCN preferred regimen)
    - In combination with lenalidomide or a granulocyte-colony stimulating factor (G-CSF) following no response (despite adequate iron stores) to an erythropoiesis-stimulating agent (ESA) alone or luspatercept-aamt
  - For individuals with no del(5q), with or without one other cytogenetic abnormalities ring sideroblasts ≥15 percent (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum erythropoietin ≤500 mU/mL following no response to luspatercept-aamt
    - As a single agent
    - In combination with a granulocyte-colony stimulating factor (G-CSF)
- Hb is less than 10 g/dL (or HCT is less than 30 percent) at the initiation of therapy.
- The intent of therapy is to maintain a Hb/HCT level no greater than 10-12 g/dL (Hb) or 30-36 percent (HCT).

†Lower risk defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate).

There are three main prognostic scoring systems. See Guidelines Section for more details.

Myelofibrosis

For individuals with anemia related to myelofibrosis when all both of the following criteria are met:

- Endogenous serum erythropoietin level less than 500mU/mL
- Hb is less than 10 g/dL (or HCT is less than 30 percent) at the initiation of therapy and one of the following:
  - With presence of symptomatic splenomegaly and/or constitutional symptoms currently controlled on a JAK inhibitor, to be given in combination with ruxolitinib
  - With no symptomatic splenomegaly and/or constitutional symptoms

Continuation of ESA Therapy for Cancer and Related Oncologic Conditions

Professional providers should use the lowest dose of ESA required to avoid red blood cell (RBC) transfusions. ESA treatment is considered medically necessary and, therefore, covered for eight weeks after the final dose of a myelosuppressive chemotherapy regimen.

NOT MEDICALLY NECESSARY CRITERIA FOR EPOETIN ALFA (EPOGEN®, PROCRIT®), RELATED BIOSIMILARS (e.g., EPOETIN ALFA-EPBX [RETACRIT™])**,** AND DARBEPOETIN ALFA (ARANESP®)
An ESA such as epoetin alfa (Epogen®, Procrit®), related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]), or darbepoetin alfa (Aranesp®) is considered not medically necessary and, therefore, not covered for any of the following indications because the available published peer-reviewed literature does not support its use:

- Anemia of cancer not related to cancer treatment
- Prophylactic use to prevent chemotherapy-induced anemia
- Prophylactic use to reduce tumor hypoxia
- Individuals with erythropoietin-type resistance due to neutralizing antibodies
- Anemia in individuals who have cancer or are undergoing cancer treatment, when anemia is due to folate deficiency, vitamin B12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
- Anemia associated with the treatment of acute or chronic myelogenous leukemia (AML, CML) or erythroid cancers
- Any anemia associated only with radiotherapy
- For individuals receiving non-myelosuppressive therapy

- For individuals with pure red cell aplasia that begins following treatment with epoetin alfa or other erythropoietin protein drugs

ANEMIA ASSOCIATED WITH NON-ONCOLOGIC CONDITIONS

MEDICALLY NECESSARY CRITERIA FOR EPOETIN ALFA (EPOGEN®, PROCRIT®), RELATED BIOSIMILARS (e.g., EPOETIN ALFA-EPBX [RETACRIT™]), AND DARBEPOETIN ALFA (ARANESP®).
Epoetin alfa (Epogen®, Procrit®), related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]), or darbepoetin alfa (Aranesp®) are considered medically necessary and, therefore, covered for the treatment of anemia associated with the following indications when the following criteria for each indication are met:

Acquired Immunodeficiency Syndrome (HIV/AIDS)

For individuals who have HIV/AIDS and anemia when all of the following criteria are met:

- Endogenous serum erythropoietin level of 500mU/mL or less that is induced by treatment with zidovudine (AZT) administered at 4,200 mg/week or less.
- Hb is less than 10g/dL or Hct is less than 30 percent at the initiation of therapy.

Chronic Kidney Disease (CKD)

For individuals who have anemia related to CKD when all of the following criteria are met:

- Hb is less than 10 g/dL (or HCT is less than 30 percent) at the initiation of therapy.
- Glomerular filtration rate (GFR) is less than 60 mL/min/1.73 m2 for 3 or more months.

MEDICALLY NECESSARY CRITERIA FOR EPOETIN ALFA (EPOGEN®, PROCRIT®) AND RELATED BIOSIMILARS (e.g., EPOETIN ALFA-EPBX [RETACRIT™])
Epoetin alfa (Epogen®, Procrit®) and related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) are considered medically necessary and, therefore, covered for the treatment of anemia associated with the following indication when the following criteria are met:

Perisurgical Adjuvant Therapy

For individuals with anemia who are undergoing elective, nonvascular, noncardiac, nonvascular surgery, when all of the following criteria are met:

- Hb is between 10-13 g/dL (or HCT is between 30-39 percent).
- The individual is at high risk for perioperative blood loss.
- The individual is not a candidate for autologous blood transfusion.
- The individual is expected to lose two or more units of blood.
- The individual has been evaluated to ensure that anemia is due to chronic disease.

CONTINUATION OF ESA THERAPY WITH EPOETIN ALFA (EPOGEN®, PROCRIT®) AND RELATED BIOSIMILARS (e.g., EPOETIN ALFA-EPBX [RETACRIT™])
During ESA therapy, many individuals eventually require supplemental iron. In order to guide appropriate supplementation, iron stores should be regularly monitored to ensure a transferrin saturation greater than 20 percent and/or serum ferritin levels greater than 100 ng/mL.

MEDICALLY NECESSARY CRITERIA FOR METHOXYPOLYETHYLENE GLYCOL-EPOETIN BETA (MIRCERA®)
Methoxypolyethylene glycol-epoetin beta (Mircera®) is considered medically necessary and, therefore, covered for the treatment of the following indications when the following criteria are met:

- Anemia associated with chronic kidney disease in adults on hemodialysis and adults not on hemodialysis
- Anemia associated with chronic kidney disease in pediatric individuals 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA

CONTINUATION OF ESA THERAPY WITH METHOXYPOLYETHYLENE GLYCOL-EPOETIN BETA (MIRCERA®)
Methoxypolyethylene glycol-epoetin beta (Mircera®) is considered medically necessary and, therefore, covered for continuation of the treatment when the following criteria are met:

- Professional providers use the lowest dose of ESA required to avoid red blood cell (RBC) transfusions. During therapy, evaluation of iron status and correction or exclusion of other causes of anemia is required.

- If Hb does not rise adequately over a 12-week escalation period: Additional dose increase is unlikely to improve response and may increase risk. Evaluate other causes of anemia and discontinue therapy if responsiveness does not improve.

NOT MEDICALLY NECESSARY CRITERIA FOR METHOXYPOLYETHYLENE GLYCOL-EPOETIN BETA (MIRCERA®)
Methoxypolyethylene glycol-epoetin beta (Mircera®) is considered not medically necessary and, therefore, not covered for any of the following indications because the available published peer-reviewed literature does not support its use:

- Treatment of anemia due to cancer chemotherapy or radiation
- Substitute for RBC transfusions in individuals who require immediate correction of anemia

NOT ELIGIBLE FOR REIMBURSEMENT
Peginesatide (Omontys®) is no longer manufactured and has been withdrawn from the market, as of February 23, 2013; therefore, it is not eligible for reimbursement. This drug was withdrawn from the market due to serious hypersensitivity reactions, which can be life-threatening.

EXPERIMENTAL/INVESTIGATIONAL

All other uses of ESA therapy are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the health care professional's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Documentation supporting the indication for ESA therapy must be maintained in the individual’s medical record and made available upon request. For all individuals, this includes:

- Assessment of, and correction for, contributing factors for anemia such as: iron deficiency, underlying infection or inflammatory process, underlying hematological diseases, hemolysis, vitamin deficiencies [e.g., folic acid, B12], blood loss, aluminum intoxication)
- Baseline Hb/HCT levels
- Date of initiation of ESA therapy
- Documentation of adequate iron stores
- Individual’s weight and ESA units administered per kilogram of body weight
- Response to ESA therapy (i.e., regular reporting of Hb/HCT to monitor response to ESA dose and documentation of transfusion requirements)
- Medical justification for exceeding recommended doses of ESA
- Additional information determined by indication

For rare instances when an individual's cardiac, pulmonary, or other medical condition warrants the use of ESA therapy to maintain an Hb/HCT higher than the target level discussed in this policy, documentation to support this practice must be available upon request.

BILLING REQUIREMENTS

Refer to the Coding Table in this policy for a list of modifier codes that are applicable to ESA therapy. When reporting ESA therapy, the most appropriate modifier that identifies this service must be used.

Guidelines

This policy is consistent with Medicare's coverage criteria. The Company's payment methodology may differ from Medicare.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, erythropoiesis-stimulating agents (ESAs) and related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in the medical policy are met.

A medication or class of medications may be a product exclusion. Individual benefits must be verified.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when ESAs are covered under a member's medical benefit (Part B benefit). It does not address instances when ESAs is covered under a member's pharmacy benefit (Part D benefit).

POTENTIAL CAUSES OF ANEMIA

Because darbepoetin alfa (Aranesp®), epoetin alfa (Epogen®, Procrit®), and related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) have a similar mode of action and their structures differ only by the number of N-linked oligosaccharides on the protein, this policy does not distinguish differences for indications and contraindications, except for pretreatment of selective surgery where blood loss is anticipated due to the long-acting nature of darbepoetin alfa (Aranesp®).

The following causes of anemia must be considered, documented, and corrected (when possible) before starting ESA therapy for the medically necessary indications listed in this policy:

- Iron deficiency
- Underlying infection or inflammatory process
- Underlying hematological disease
- Hemolysis
- Vitamin deficiencies (e.g., folic acid, B_{12})
- Blood loss
- Aluminum intoxication

ESA DOSAGE ADJUSTMENTS FOR CANCER AND RELATED NEOPLASTIC CONDITIONS

- During ESA therapy, many individuals eventually require supplemental iron. To guide appropriate supplementation, iron stores should be regularly monitored to ensure a transferrin saturation greater than 20 percent and/or serum ferritin levels greater than 100 ng/mL.
- ESA doses must be titrated according to the individual's response.

<table>
<tr><th colspan="5">ESA DOSING AND TITRATION FOR CANCER AND RELATED NEOPLASTIC CONDITIONS</th></tr>
<tr><th></th><th colspan="2">EPOETIN ALFA
(AND BIOSIMILARS)</th><th colspan="2">DARBEPOETIN ALFA</th></tr>
<tr><td>INITIAL DOSE</td><td>Adult:150 U/kg SQ 3 times wkly
Pediatric: 600 U/kg IV wkly</td><td>Adult: 40,000 U SQ wkly*
Pediatric: 600 U/kg IV wkly</td><td>2.25 mcg/kg SQ wkly</td><td>500 mcg SQ every 3 wks</td></tr>
<tr><td>MAINTENANCE DOSE</td><td colspan="2">If Hb remains <10 g/dL (or HCT is <30%) compared to pretreatment baseline 4 wks after initiation of therapy, and the rise in Hb is ≥1 g/dL (or HCT is ≥3%), the maintenance dose of ESA therapy should be the same as the recommended FDA starting dose.</td><td colspan="2">(Same as Epoetin Alfa)</td></tr>
<tr><td rowspan="2">DOSE INCREASE</td><td colspan="2">If Hb rises <1 g/dL (or HCT rises <3%) compared to pretreatment baseline 4 wks after initiation of therapy, and Hb remains <10 g/dL (or HCT is <30%).</td><td colspan="2">If Hb rises <1 g/dL (or HCT rises <3%) compared to pretreatment baseline 6 wks after initiation of therapy, and Hb remains <10 g/dL (or HCT is <30%).</td></tr>
<tr><td>Adult: 300 U/kg SQ 3 times wkly
Pediatric: 900 U/kg</td><td>Adult: 60,000 U SQ wkly**</td><td>4.5 mcg/kg SQ wkly</td><td>No dose adjustment</td></tr>
</table>

	(max 60,000 units) IV wkly	Pediatric: 900 U/kg (max 60,000 units) IV wkly		
DOSE REDUCTION	If Hb rises >1 g/dL (or HCT rises >3%) in any 2-wk period, reduce dose by 25%. If Hb reaches a level needed to avoid red blood cell (RBC) transfusion, reduce dose by 25%. If Hb exceeds a level needed to avoid RBC transfusion, withhold dose. When Hb approaches a level requiring RBC transfusion, reinitiate dose 25% below previous dose.		If Hb rises >1 g/dL (or HCT rises >3%) in any 2-wk period, reduce dose by 40%. If Hb reaches a level needed to avoid RBC transfusion, reduce dose by 40%. If Hb exceeds a level needed to avoid RBC transfusion, withhold dose. When Hb approaches a level requiring RBC transfusion, reinitiate dose 40% below previous dose.	
DOSE DISCONTINUATION	Continuation of ESA therapy is not warranted if there is a rapid rise in Hb >1 g/dL (or HCT rises >3%) over any 2-wk period of treatment unless the Hb remains below or subsequently falls to <10 g/dL (or HCT is <30%). In these cases, continuation or reinstitution of ESA therapy must include a dose reduction from the previously administered dose of 25%. Continuation of ESA therapy is not warranted if after 8 wks of treatment, the Hb rises <1 g/dL (or HCT rises <3%) compared to pretreatment baseline or if RBC transfusions are still required after 8 wks of treatment.		Continuation of ESA therapy is not warranted if there is a rapid rise in Hb >1 g/dL (or HCT rises >3%) over any 2-wk period of treatment unless the Hb remains below or subsequently falls to <10 g/dL (or HCT is <30%). In these cases, continuation or reinstitution of ESA therapy must include a dose reduction from the previously administered dose of 40%. Continuation of ESA therapy is not warranted if after 8 wks of treatment, the Hb rises <1 g/dL (or HCT rises <3%) compared to pretreatment baseline or if RBC transfusions are still required after 8 wks of treatment.	

* According to the US Food and Drug Administration (FDA)-approved prescribing information, individuals 5 to 18 years of age have a recommended starting dose of 600 U/kg intravenously weekly.

** According to the FDA-approved prescribing information, individuals 5 to 18 years of age should increase the dose to 900 U/kg (maximum 60,000 U) weekly if after 4 weeks of initiation of epoetin alfa or related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) the hemoglobin increases less than 1 g/dL and remains below 10 g/dL.

ESA DOSAGE ADJUSTMENTS FOR CHRONIC KIDNEY DISEASE (CKD) AND END-STAGE RENAL DISEASE (ESRD)

- Healthcare professionals and individuals should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.
- Use the lowest dose sufficient to reduce the need for RBC transfusions.
- Consider initiating treatment when the rate of Hb decline indicates the likelihood of requiring a RBC transfusion.
- Consider initiating treatment when reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

ESA DOSING AND TITRATION FOR CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE					
	EPOETIN ALFA (AND BIOSIMILARS)	**DARBEPOETIN ALFA**	**METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA**		
			Adults	Pediatrics on hemodialysis converting from	
INITIAL DOSE	Adults: 50–100 U/kg IV or SQ 3 times wkly Pediatrics: 50 U/kg IV or SQ 3 times wkly	Adults on Dialysis: 0.45 mcg/kg IV or SQ wkly or 0.75 mcg/kg IV every 2 wks Pediatric: 0.45 mcg/kg IV or SQ wkly Not on Dialysis: Adult: 0.45 mcg/kg IV or SQ once at 4-wk intervals Pediatric: 0.75	0.6 mcg/kg IV or SQ every 2 weeks	Epoetin alfa: 4 × previous weekly epoetin alfa dose (Units) /125	Darbepoetin: 4 × previous weekly darbepoetin alfa dose (mcg)/0.55

		mcg/kg IV or SQ every 2 weeks			
DOSE INCREASE	If Hb rises <1 g/dL (or HCT rises <3%) compared to pretreatment baseline 4 wks after initiation of therapy, and Hb remains <10 g/dL (or HCT is <30%), the recommended FDA starting dose may be increased by 25%. Dose should not be increased more than once every 4 weeks, but may be decreased more frequently. Avoid frequent dose adjustments.				
DOSE REDUCTION	If Hb rises >1 g/dL (or HCT rises >3 %) in any 2-wk period, the ESA dose must be reduced by ≥25% as needed. If Hb >10 g/dL in those NOT on dialysis or if Hb ≥11 g/dL in those on dialysis, the ESA dose must be interrupted or reduced.				
DOSE DISCONTINUATION	If adequate response is not achieved after a 12-wk escalation period, increasing the ESA is unlikely to improve response and may increase risks. Evaluate other causes of anemia. Discontinue ESA if responsiveness does not improve.				

DOSING GUIDELINES FOR MYELODYSPLASTIC SYNDROME

- Hb must have a 1 g/dL sustained increase when compared to initiation level by the 12th week of therapy to continue therapy.

MYELODYSPASTIC SYNDROME PROGNOSTIC SCORING SYSTEMS

There are three main prognostic scoring systems:

- International Prognostic Scoring System (IPSS)
- Revised International Prognostic Scoring System (IPSS-R)
- WHO classification-based Prognostic Scoring System (WPSS)

The IPSS-R enhances prognostic risk stratification is applicable to the general MDS population. IPSS-R Cytogenetic risk is based on cytogenic abnormalities as follows:

IPSS-R Cytogenetic risk groups†,††

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values†

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

IPSS-R Prognostic Risk Categories/Scores†

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3

Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

†Greenberg PL, Tüchler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2460.

††Schanz J, Tüchler J, Solé F, et al. *J Clin Oncol*. 2012;30:820-829.

BLACK BOX WARNINGS

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Initial approval for the use of epoetin alfa (Epogen®, Procrit®) as an ESA was granted by the FDA on June 1, 1989. Supplemental approvals have since been issued.

Initial approval for the use of darbepoetin alfa (Aranesp®) as an ESA was granted by the FDA on September 19, 2001. Supplemental approvals have since been issued.

Initial approval for the use of methoxy polyethylene glycol-epoetin beta (Mircera®) as an ESA was granted by the FDA on November 14, 2007. Supplemental approvals have since been issued.

Initial approval for the use of peginesatide (Omontys®) as an ESA was granted by the FDA on March 27, 2012.

On February 23, 2013, Affymax, Inc. and Takeda Pharmaceutical Company Limited, in conjunction with the FDA, initiated a voluntary recall of all lots of peginesatide (OMONTYS®) injection to the individual level due to recent postmarketing reports regarding serious hypersensitivity reactions, including anaphylaxis, which can be life-threatening or fatal. As of August 2013, per the Pharmaceutical Companies, peginesatide (OMONTYS®) injection was still unavailable for prescribing or dispensing by healthcare professionals.

Initial approval for the use of biosimilar epoetin alfa-epbx (Retacrit™) as an ESA was granted by the FDA on May 15, 2018. Epoetin alfa (Epogen®, Procrit®) are the reference products for this biosimilar.

Description

Erythropoietin is a hormone that is produced by the kidneys, primarily in response to hypoxia. Its purpose is to stimulate bone marrow to form new red blood cells, a process called erythropoiesis. When the kidneys cannot produce enough erythropoietin, an erythropoiesis-stimulating agent (ESA) is prescribed to mimic its action. An ESA is used in the treatment of certain types of anemia to elevate or maintain the individual's red blood cell level (as demonstrated by the hemoglobin [Hb] and/or hematocrit [HCT] levels) and to decrease the need for transfusions.

Darbepoetin alfa (Aranesp®), epoetin alfa (Epogen®, Procrit®) and related biosimilars (e.g., epoetin alfa-epbx [Retacrit™]) are biologically engineered hormones produced by recombinant deoxyribonucleic acid (DNA) technology. They are erythropoietin analogs that contain the identical amino acid sequence as naturally occurring erythropoietin and have the same biological effect. Darbepoetin alfa (Aranesp®) differs from recombinant human epoetin alfa (Epogen®, Procrit®) by having two additional N-glycosylation sites. This slows the drug's clearance and makes its half-life two to three times longer, thereby requiring less frequent injections.

Methoxypolyethylene glycol-epoetin beta (Mircera®) was approved by the US Food and Drug Administration (FDA) for anemia associated with chronic kidney disease in adults, including individuals on dialysis and not on dialysis and pediatric individuals 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. Methoxypolyethylene glycol-epoetin beta (Mircera®) is not indicated for the treatment of anemia due to cancer chemotherapy and is not a substitute for red blood cell transfusions in individuals who require immediate correction of anemia. Methoxypolyethylene glycol-epoetin beta (Mircera®) is an erythropoietin receptor activator with a greater activity and increased half-life compared to erythropoietin.

Peginesatide (Omontys®) is a synthetic, nonrecombinant peptide whose structure is unrelated to endogenous human erythropoietin. On February 23, 2013, Affymax, Inc. and Takeda Pharmaceutical Company Limited, in conjunction with the FDA, initiated a voluntary recall of all lots of peginesatide (OMONTYS®) injection to the patient level due to recent postmarketing reports regarding serious hypersensitivity reactions, including anaphylaxis, which can be life-threatening or fatal. As of May 2014, peginesatide is currently unavailable for prescribing or dispensing by healthcare professionals.

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
D61.1 Drug-induced aplastic anemia
D63.1 Anemia in chronic kidney disease
D63.8 Anemia in other chronic diseases classified elsewhere
D64.81 Anemia due to antineoplastic chemotherapy

HCPCS Level II Code Number(s)
J0881 Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882 Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
J0885 Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non ESRD use)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units
Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

NOT ELIGIBLE FOR REIMBURSEMENT

THE FOLLOWING CODE REPRESENTS J0890 WHICH IS NO LONGER MANUFACTURED AND HAS BEEN WITHDRAWN FROM THE MARKET
J0890 Injection, peginesatide, 0.1 mg (for ESRD on dialysis)

Revenue Code Number(s)
0634 Pharmacy - Extension - Erythropoietin (EPO) Less Than 10,000 Units
0635 Pharmacy - Extension - Erythropoietin (EPO) 10,000 or More Units

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Modifiers

EA Erythropoetic stimulating agent (ESA) administered to treat anemia due to anticancer chemotherapy
EB Erythropoetic stimulating agent (ESA) administered to treat anemia due to anticancer radiotherapy
EC Erythropoetic stimulating agent (ESA) administered to treat anemia not due to anticancer radiotherapy or anticancer chemotherapy
EJ Subsequent claims for a defined course of therapy, e.g., EPO, sodium hyaluronate, infliximab
GS Dosage of EPO or darbepoetin alfa has been reduced and maintained in response to hematocrit or hemoglobulin level

THE FOLLOWING CODES ARE MEDICALLY NECESSARY WHEN REPORTED WITH EA: Erythropoetic stimulating agent (ESA) administered to treat anemia due to anticancer chemotherapy

J0881 Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0885 Injection, epoetin alfa, (for non-ESRD use), 1000 units
Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

THE FOLLOWING CODES ARE NOT MEDICALLY NECESSARY WHEN REPORTED WITH EA: Erythropoetic stimulating agent (ESA) administered to treat anemia due to anticancer chemotherapy

J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non ESRD use)

THE FOLLOWING CODES ARE NOT MEDICALLY NECESSARY WHEN REPORTED WITH EB: Erythropoetic stimulating agent (ESA) administered to treat anemia due to anticancer radiotherapy.

J0881 Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882 Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
J0885 Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non ESRD use)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units
Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

THE FOLLOWING CODES ARE MEDICALLY NECESSARY WHEN REPORTED WITH EC: Erythropoetic stimulating agent (ESA) administered to treat anemia not due to anticancer radiotherapy or anticancer chemotherapy

J0881 Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882 Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
J0885 Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non ESRD use)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units
Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

THE FOLLOWING CODES AND MODIFIERS ARE NOT MEDICALLY NECESSARY WHEN REPORTED WITHOUT EA, EB OR EC MODIFIER

J0881 Injection, darbepoetin alfa, 1 mcg (non-ESRD use)
J0882 Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
J0885 Injection, epoetin alfa, (for non-ESRD use), 1000 units
J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)
J0888 Injection, epoetin beta, 1 microgram, (for non ESRD use)
Q4081 Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units
Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units
EJ Subsequent claims for a defined course of therapy, e.g., EPO, sodium hyaluronate, infliximab
GS Dosage of EPO or darbepoetin alfa has been reduced and maintained in response to hematocrit or hemoglobulin level

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Policy History

Revisions From MA08.011f:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	The policy has been updated to communicate changes based on US Food and Drug Administration (FDA) labeling and the National Comprehensive Cancer Network (NCCN). Criteria have been added to the policy: • Chemotherapy-induced anemia Criteria have been revised for:

	• Myelodysplastic Syndrome • Perisurgical adjuvant therapy • Therapy for cancer and related oncologic conditions Criteria have been removed for: • Hepatitis C
08/24/2022	This policy has been reissued in accordance with the Company's annual review process.
09/27/2021	This version of the policy will become effective 09/27/2021. The policy has been updated to communicate changes based on US Food and Drug Administration (FDA) labeling and the National Comprehensive Cancer Network (NCCN). Criteria have been revised for: • Myelodysplastic Syndrome. • Perisurgical Adjuvant Therapy • Therapy for Cancer and Related Oncologic Conditions Criteria have been removed for Acute Kidney Injury

Revisions From MA08.011e:

06/03/2020	This policy has been reissued in accordance with the Company's annual review process.
01/01/2020	This policy has been identified for the HCPCS code update, effective 01/01/2020. The following HCPCS codes have a **revised narrative** in this policy: **FROM** Q5105 Injection, epoetin alfa, biosimilar, (Retacrit) (for ESRD on dialysis), 100 units **TO** Q5105 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for esrd on dialysis), 100 units **FROM** Q5106 Injection, epoetin alfa, biosimilar, (Retacrit) (for non-ESRD use), 1000 units **TO** Q5106 Injection, epoetin alfa-epbx, biosimilar, (retacrit) (for non-esrd use), 1000 units

Revisions From MA08.11d:

09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
01/28/2019	This version of the policy will become effective 01/28/2019. The policy has been updated to communicate changes based on US Food and Drug Administration (FDA) labeling and the National Comprehensive Cancer Network (NCCN). Criteria have been revised to include biosimilar epoetin alfa-epbx (Retacrit™) as an ESA. Not medically necessary criteria have been revised for all agents. Criteria for methoxy polyethylene glycol-epoetin beta (Mircera®) was updated to include indications for pediatric individuals, continuation therapy recommendations, and not medically necessary criteria. Criteria for myelodysplastic syndrome were updated per NCCN. _____ ***Note***: On 04/08/2019 the Miscellaneous Coding - Modifiers section of the Coding Table was revised to clarify which codes should be used with the EC Modifier. • Codes J0881, J0885, Q5106 were added as medically necessary when reported with EC. They were listed as not medically necessary in error. • The listing of codes considered not medically necessary when reported without the EC Modifier was removed because it was duplicative.

	These changes are retroactively effective to 01/28/2019.

Revisions From MA08.011c:

05/31/2017	This policy has been updated to be consistent with the US Food and Drug Administration (FDA) labeling and NCCN compendia. Coverage was added for the condition of myelofibrosis with criteria. Criteria was removed for the conditions of rheumatoid arthritis and anemia of prematurity. Dosing guidelines were updated to include pediatric dosing for epoetin alfa for cancer and related neoplastic conditions. Dosing guidelines for chronic kidney disease and end stage renal disease were also updated to include pediatric dosing for darbepoetin alfa and dosing for methoxy polyethylene glycol-epoetin beta. REMS requirement was removed from the description. The following ICD-10 diagnosis codes will be removed: D46.0, D46.1, D46.20, D46.21, D46.22, D46.4, D46.9, D46.A, D46.B, D46.C, D46.Z, D61.810, D61.811, D64.9, P61.2

Revisions From MA08.011b:

02/08/2016	This version of the policy will become effective 02/08/2016. The policy criteria for methoxypolyethylene glycol-epoetin beta (Mircera®) for chronic kidney disease was **updated** to be consistent with US Food and Drug Administration (FDA) Labeling and Drug Compendia. The policy criteria for epoetin alfa (Epogen®, Procrit®) and darbepoetin alfa (Aranesp®) for slect chronic diseases and Acquired Immunodeficiency Syndrome (AIDS) was **updated** to be consistent with US Food and Drug Administration (FDA) Labeling and Drug Compendia.

Revisions From MA08.011a:

01/01/2016	This policy has been identified for the HCPCS code update, effective 01/01/2016. The following HCPCS code has been **deleted** from this policy: J0886

Revisions From MA08.011:

01/01/2015	This is a new policy. The following HCPCS codes have been **deleted** from this policy: Q9972 Injection, Epoetin Beta, 1 microgram, (For ESRD On Dialysis) Q9973 Injection, Epoetin Beta, 1 microgram, (Non-ESRD use) The following HCPCS code has been **added** to this policy: J0887 Injection, epoetin beta, 1 microgram, (for ESRD on dialysis) J0888 Injection, epoetin beta, 1 microgram, (for nonESRD use)

Version Effective Date:
05/07/2024
Version Issued Date:
05/07/2024
Version Reissued Date:
03/28/2025