


MEDICAL POLICY – 5.01.535

Erythropoiesis-Stimulating Agents

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Introduction

Red blood cells are made inside the bone marrow. The process of making red blood cells is called “erythropoiesis”. If there are not enough red blood cells in the body, a person is said to be anemic. The kidneys make a hormone called “erythropoietin” that stimulates the bone marrow to make more red blood cells. Drugs called ESAs (erythropoiesis-stimulating agents) are similar to our own erythropoietin. These drugs can be used to stimulate the bone marrow to make more red blood cells. This policy describes when the use of ESAs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Indication	Medical Necessity
Anemia due to chronic	The use of epoetin alfa, epoetin alfa-epbx, darbepoetin, or

Indication	Medical Necessity
<p>kidney disease (CKD)</p>	<p>pegylated (PEG)-epoetin beta may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Treatment of anemia associated with chronic kidney disease^{a,b,c,d} <p>For medically necessary use in patients with chronic kidney disease the following must be documented:</p> <ul style="list-style-type: none"> • For initial ESA therapy, Hb level below 10 g/dL must be documented within 1 month prior to initial ESA administration and Hb levels should be repeated at least monthly during maintenance phase of therapy.^{15,33,34} • For ongoing ESA therapy, Hb level below 12 g/dL is considered acceptable as 11.0 to 11.9 is the target range for Hb level. • If on dialysis (hemodialysis or peritoneal): Documentation of adequate iron stores by transferrin saturation ($\geq 20\%$) or ferritin level (> 400 ng/mL) within 1 month of initiating ESA is required.³³ • If not on dialysis (hemodialysis or peritoneal); Documentation of adequate iron stores by transferrin saturation ($\geq 20\%$) or ferritin level (> 200 ng/mL) within 1 month of initiating ESA is required.³³ • When ferritin levels are >500 ng/mL, the test is unreliable as a basis for IV iron therapy, and other measures should be considered including ESA responsiveness, clinical status, Hb and TSAT levels. • If adequate iron stores are not present, iron administration aimed at achieving adequate iron stores is required; this may be done at same treatment session as ESA administration.¹¹ • Repeat documentation of adequate iron stores is required during ongoing ESA therapy using levels defined above. <p>The use of PEG-epoetin beta is investigational for all other indications; it does not have Food and Drug Administration (FDA) approval for any other indication</p> <p>^aFDA-approved label for epoetin alfa (Epogen®, Procrit®) ^bFDA-approved label for darbepoetin alfa (Aranesp®)</p>



Indication	Medical Necessity
	<p>^cFDA-approved label for PEG-epoetin beta (Mircera®) ^dFDA-approved label for epoetin alfa-epbx (Retacrit™)</p>
<p>Anemia due to other conditions</p>	<p>The use of epoetin alfa, epoetin alfa-epbx, or darbepoetin may be considered medically necessary for the following:</p> <ul style="list-style-type: none"> • Treatment of anemia in cancer patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy^{a,b,c} <ul style="list-style-type: none"> ○ Therapy should not be initiated at Hb levels of 10 g/dL or higher <p>AND</p> <ul style="list-style-type: none"> ○ Treatment should be discontinued after completion of a myelosuppressive chemotherapy course <ul style="list-style-type: none"> • Treatment of anemia related to therapy with AZT (zidovudine) in HIV-infected patients^{a,c} • Reduction of allogeneic blood transfusion in surgery patients^{a,c} • Treatment of patients after allogeneic bone marrow transplantation • Treatment of patients with myelodysplastic syndromes to reduce transfusion dependency • Treatment of patients with hepatitis C and anemia related to ribavirin treatment <p>Note: Documentation of iron stores in oncology patients is indicated only if there is no improvement in hemoglobin (Hb) level with ESA use.</p> <p>In the medically necessary conditions noted above, all of the following criteria also apply:</p> <ul style="list-style-type: none"> • The lowest dose of erythropoiesis-stimulating agent (ESAs) should be used in order to avoid red blood cell transfusions • ESAs should not be used to raise the hemoglobin (Hb) level above 12 g/dL; (target Hb levels should be in the range of 11.0 to 11.9 g/dl) • ESA therapy should not be administered without adequate iron stores <p>^aFDA-approved label for epoetin alfa (Epogen®, Procrit®) ^bFDA-approved label for darbepoetin alfa (Aranesp®) ^cFDA-approved label for epoetin alfa-epbx (Retacrit™)</p>



Indication	Investigational
Anemia after high-dose chemotherapy or associated with cancer	<p>Epoetin alfa, epoetin alfa-epbx, or darbepoetin is considered investigational for:</p> <ul style="list-style-type: none"> • Treatment of patients after high-dose chemotherapy with autologous stem-cell support • Treatment of non-iatrogenic chronic anemia of cancer • Other cancer-associated anemia excepted as noted above

Documentation Requirements
<p>The patient's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:</p> <ul style="list-style-type: none"> • Diagnosis/condition • History and physical examination documenting the severity of the condition • Recent (within the past month) hemoglobin level • For patients with chronic kidney disease: <ul style="list-style-type: none"> ○ Recent (within the past month) ferritin level or transferrin saturation ○ Whether or not the patient is receiving dialysis

Coding

Code	Description
HCPCS	
J0881	Injection, darbepoetin alfa (Aranesp®), 1 mcg (non-ESRD use)
J0882	Injection, darbepoetin alfa (Aranesp®), 1 microgram (for ESRD on dialysis)
J0885	Injection, epoetin alfa (Epogen®, Procrit®), (for non-ESRD use), 1000 units
J0887	Injection, epoetin beta (Mircera®), 1 microgram, (for ESRD on dialysis)
J0888	Injection, epoetin beta (Micera®), 1 microgram, (for non-ESRD use)
Q4081	Injection, epoetin alfa (Epogen®, Procrit®), 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



Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Throughout this policy, unless otherwise stated:

- The term ESA refers to three drugs: epoetin alfa (brand names Epogen® [Amgen, Thousand Oaks, CA] and Procrit® [Janssen Product, LP, Titusville, NJ]), epoetin alfa-epbx (brand name Retacrit™ [Pfizer, New York, NY]) and darbepoetin alfa (brand name Aranesp® [Amgen, Thousand Oaks, CA])
- Non-myeloid malignancies include solid tumors and the non-myeloid hematologic malignancies of myeloma, lymphoma, and chronic lymphocytic leukemia

Administration

ESAs and pegylated (PEG)-epoetin beta are to be administered according to current FDA-approved labeling for each product, using recommended hemoglobin (Hb) levels for determining when to start, stop, and adjust the dose. This includes decreasing the dose of ESA as the Hb approaches the target level.

Before commencing ESA or PEG-epoetin beta therapy, the patient's iron stores, blood ferritin, and transferrin saturation should be evaluated, adjusted, and maintained within normal physiological limits. ESA or PEG-epoetin beta therapy should not be administered without adequate iron stores.

Blood Pressure Monitoring

Blood pressure should be adequately controlled before initiation of ESA therapy and closely monitored and controlled during treatment. ESAs and PEG-epoetin beta are contraindicated in patients with uncontrolled hypertension.



Discontinuation

Erythropoiesis-Stimulating Agents (ESA)

Patients with myelodysplastic syndromes should be initially limited to a 3-month trial period with ESA. If no response to ESA is observed, ongoing therapy would be futile.

ESAs and PEG-Epoetin Beta

Patients with chronic kidney disease (CKD) who do not respond adequately over a 12-week dose escalation period should not have their ESA or PEG-epoetin beta dose increased further. Increasing ESA or PEG-epoetin beta dose further is unlikely to improve response and may increase risks; the lowest ESA or PEG-epoetin beta dose that maintains adequate hemoglobin (Hb) to avoid recurrent red blood cell transfusions should be used. Other causes of anemia should be evaluated. If responsiveness does not improve, discontinue ESA or PEG-epoetin beta therapy.

Epoetin alfa and darbepoetin alfa REMS

Prior data suggested that patients had worse outcomes when epoetin alfa and darbepoetin alfa were used in cancer patients or when these drugs were used to increase hemoglobin levels above 11 g/dl in patients with ESRD. This led to an FDA sponsored REMS program between 2011 and 2017.

In April 2017, the FDA eliminated the REMS for Epogen®/Procrit® and Arenesp®, stating that “the risks can be communicated by the current product prescribing information” and that “The appropriate use of ESAs is supported by the Centers for Medicare and Medicaid Services’ (CMS) National Coverage Determination, the American Society of Clinical Oncology, the American Society of Hematology clinical guidelines, which are evidence-based guidelines intended to provide a basis for the standard of care in clinical oncology.”

PEG-epoetin beta does not have an REMS.

In 2012, the FDA approved an REMS for peginesatide, however this drug is no longer in use.

Peginesatide is currently discontinued.



Description

Endogenous erythropoietin is a glycoprotein hematopoietic growth factor that regulates hemoglobin levels in response to changes in the blood oxygen concentration. Erythropoiesis-stimulating agents (ESAs; eg, epoetin alfa, epoetin alfa-epbx, pegylated epoetin beta, darbepoetin) are produced using recombinant DNA technologies and have pharmacologic properties similar to endogenous erythropoietin. The primary clinical use of ESAs is to treat chronic anemia.

Background

Endogenous Erythropoietin and Anemia

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor synthesized by cells near the renal tubules in response to changes in the blood oxygen concentration. When a patient is anemic, the ability of the blood to carry oxygen is decreased. An oxygen-sensing protein in the kidney detects the decrease in blood oxygen concentration and induces the production of EPO, which then acts on the erythroid cell line in the bone marrow to stimulate hematopoiesis, thereby effectively increasing blood hemoglobin (Hb) concentrations. Suppression of erythropoietin production or suppression of the bone marrow response to erythropoietin results in anemia in several disease processes, including chronic kidney disease (CKD), many types of cancer treatment, other chronic diseases, and use of certain drugs.

The severity of anemia is defined by blood Hb concentration. Normal ranges are 12 to 16 g/dL in women and 14 to 18 g/dL in men. Mild anemia is defined as Hb from 10 g/dL to the lower limit of normal ranges, moderate anemia is 8 to 10 g/dL, and severe anemia is 8 g/dL or less.

Treatment

Erythropoiesis-stimulating agents are produced using recombinant DNA technologies. They were initially developed as replacement therapy to treat anemia due to endogenous erythropoietin deficiency that commonly occurs in patients with chronic renal failure (CRF) secondary to CKD¹. Patients with CRF will become severely anemic and experience severe fatigue

and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia by ESA treatment of patients with CRF reduces the need for red blood cell (RBC) transfusions and enhances physical functioning.

In cancer, anemia occurs with varying degrees of frequency and severity. It occurs most commonly in genitourinary, gynecologic, lung, and hematologic malignancies. Anemia may be directly related to cancer type or to its treatment. Oncologic anemia occurs by a variety of mechanisms:

1. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B₁₂) essential for RBC production.
2. Antibodies and/or immunoregulatory abnormalities associated with certain tumor types (most commonly, B cell malignancies) may cause increased erythrocyte destruction (hemolysis).
3. Tumors may cause blood loss via tissue invasion (eg, gastrointestinal bleeding from colon cancer).
4. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment.
5. In more advanced cases, there may be marrow replacement with tumor or amyloid.
6. However, marrow dysfunction can occur even in the absence of frank invasion.
7. Inflammatory proteins from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization, as well as a direct suppression of RBC production.

Cancer treatments also may cause anemia: (1) radical cancer surgery can result in acute blood loss; and (2) radiotherapy and many cytotoxic chemotherapeutic agents suppress marrow to varying degrees. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage; antimetabolites damage DNA indirectly; and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.

RBC transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, this approach carries risk for several potential adverse events. The highest adverse event risk (occurring in 1 per 432 whole blood units transfused) is for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (eg, type mismatch) are estimated to occur at a rate of 1 per 5,000 to 10,000 units of blood transfused. Current transfusion medicine and blood bank practices have significantly reduced the risk of transmissible infections, primarily due



to better donor selection and screening for infectious diseases. Estimated risks per unit of blood transfused for transmission of hepatitis B virus (<1 in 400,000), hepatitis C virus (<1 in 1,000,000), HIV (<1 in 1,000,000), and bacterial contaminants (1 per 10,000 to 100,000) have fallen dramatically since the early 1990s. Therefore, although the initial impetus to commercialize erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those risks. Nonetheless, blood shortages, transfusion errors, and risks of alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Five ESA products have been licensed in the United States:

- Epoetin alfa is manufactured, distributed, and marketed by Amgen, Inc. under the proprietary name, Epogen®. The same epoetin alfa product manufactured by Amgen Inc. is also marketed and distributed by Janssen Products, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit®. Under a contractual agreement with Amgen, Janssen Products LP has rights to develop and market Procrit® for any indication other than for treatment of anemia associated with CRF in patients on dialysis or use in diagnostic test kits. Epogen® and Procrit® have identical labeling information for all FDA-approved indications.
- A second ESA, epoetin alfa-epbx is manufactured by Hospira, Inc, which is a subsidiary of Pfizer Inc. Epoetin alfa-epbx is a biosimilar of Epogen®/Procrit® and has the identical FDA approved indications as Epogen®/Procrit®.
- A third ESA, darbepoetin alfa, is marketed solely by Amgen, under the proprietary name, Aranesp®.
- The fourth ESA product, peginesatide, was codeveloped and commercialized by Affymax Inc. and Takeda Pharmaceuticals, who market it under the proprietary name, Omontys®. In 2013, Affymax, Takeda, and the FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. The FDA currently lists peginesatide (Omontys®) as discontinued.
- Epoetin beta is currently unavailable in the U.S. However, a methoxy pegylated (PEG) form of epoetin beta, called “continuous erythropoietin receptor activator” or CERA, has a prolonged half-life that permits once monthly dosing. PEG-epoetin beta was FDA-approved in 2007 under the brand name Mircera®. Mircera sales in the U.S. were prohibited from 2009 until 2015 due to a copyright infringement lawsuit, however, Hoffmann-LaRoche is now manufacturing and supplying the drug to Galencia, and it is currently available.



Summary of Evidence

For individuals who have chronic kidney disease and anemia who receive epoetin alfa, epoetin alfa-epbx, pegylated epoetin beta, or darbepoetin, the evidence includes randomized controlled trials (RCTs) and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, medication use, and treatment-related mortality and morbidity. All 3 ESAs have been studied and approved for this use. Most of the evidence has demonstrated an increase in hemoglobin and a decrease in blood transfusions but has failed to demonstrate any significant improvement in clinical outcomes such as mortality and morbidity. The evidence is inconsistent in showing improvements in functional status and quality of life. Many studies have demonstrated increased mortality risk and increased risk for venous access thrombosis and stroke, prompting FDA warnings. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have cancer-related anemia who receive epoetin alfa, epoetin alfa-epbx or darbepoetin, the evidence includes RCTs, comparative analyses, and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, medication use, and treatment-related mortality and morbidity. The available trials have demonstrated an increase in hemoglobin concentration and a decrease in the need for blood transfusions. However, the evidence has also demonstrated increased mortality rates and possible tumor promotion, as well as increased risk of thromboembolic events when target hemoglobin levels were above 12 g/dL. Comparative analyses have shown that when the target hemoglobin level was lowered to 10 g/dL, patients experienced increased hemoglobin and decreased risk for blood transfusions. Length of follow-up was short in the comparative analyses, and mortality and adverse events were therefore not addressed. Epoetin alfa, epoetin alfa-epbx and darbepoetin are the ESAs approved for use in treatment of cancer-related anemia; pegylated epoetin beta is not FDA approved for this indication, because studies have demonstrated increased mortality and no significant improvement in clinical outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatitis C infection treated with ribavirin who receive epoetin alfa, epoetin alfa-epbx or darbepoetin, the evidence includes RCTs. Relevant outcomes are quality of life and medication use. Evidence from RCTs demonstrates that treatment with ESAs improves the ability to maintain full-dosing of ribavirin, because anemia is often a limiting effect for treatment. There may also be a positive effect on quality of life, although this is less certain. Epoetin alfa, epoetin alfa-epbx and darbepoetin are the ESAs approved for this use. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.



Ongoing and Unpublished Clinical Trials

Currently unpublished trials that might influence this review are listed in [Table 1](#).

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01581073	Prevention of End Stage Kidney Disease by Darbepoetin Alfa in Chronic Kidney Disease Patients with nondiabetic Kidney Disease (PREDICT)	476	Jun 2017 (ongoing)
NCT00773513^a	A Randomized, Controlled, Open Label, Multicenter, Parallel Group Study to Assess All-cause Mortality and Cardiovascular Morbidity in Patients with Chronic Kidney Disease on Dialysis and Those Not on Renal Replacement Therapy Under Treatment with Mircera® or Reference ESAs	2828	Jul 2017 (ongoing)
NCT02890602	A Phase II Study of Erythropoietin for Management of Anemia Caused by Chemotherapy in Patients with Diffuse Large B-Cell Lymphoma	53	Dec 2017
NCT02052310^a	Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients (Himalayas)	900	Mar 2018
NCT03010579	Efficacy and Safety of Erythropoietin in the Treatment of Anemia in Patients with Lymphoma after Autologous Stem Cell Transplantation	70	Dec 2018
NCT00338286	A Randomized Open Label, Multicenter, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anemic Patients with Metastatic Breast Cancer Receiving Standard Chemotherapy	2098	Jun 2019
Unpublished			
NCT00157300	PROTECT: Prospective Trial on Erythropoietin in Clinical Transplantation	92	Jul 2010 (completed)
NCT00560274^a	A study of NeoRecormon (Epoetin Beta) in Anemic Patients with Chronic Hepatitis C	190	Nov 2011 (completed)



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01383460	Efficacy of Granulocyte Colony-stimulating Factor and Erythropoietin for Patients with Acute-on-chronic Liver Failure	55	Jan 2013 (completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 academic medical centers and 2 specialty societies while this policy was under review in 2012. Reviewers agreed with the current medically necessary indications. There was support for treatment of patients with hepatitis C and ribavirin-related anemia. For investigational indications, reviewers agreed with the current policy statements.

Practice Guidelines and Position Statements

National Kidney Foundation

In 2012, the National Kidney Foundation published the “2012 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guidelines for Anemia in Chronic Kidney Disease” (CKD).⁶⁰ A consensus of an international group of experts created comprehensive, evidence-based guidance for the treatment of anemia in CKD. The Kidney Disease: Improving Global Outcomes recommendation on initiation and maintenance of erythropoiesis-stimulating agents (ESAs) was based on balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (eg, stroke, vascular access loss, hypertension). Recommendations for treatment initiation and maintenance are listed in [Table 2](#).



Table 2. Recommendations for Initial and Maintenance Therapy for Anemia in CKD

Recommendation	LOR
Initial therapy	
"We recommend using ESA therapy with great caution, if at all, in CKD patients with:	
•active malignancy	1B
•... a history of stroke or	1B
•a history of malignancy	2C
"For adult CKD ND patients with Hb concentration ≥ 10.0 g/dl (≥ 100 g/l) we suggest that ESA therapy not be initiated."	2D
"For adult CKD ND [non-dialysis] patients with Hb [hemoglobin] concentration ≤ 10.0 g/dl (< 100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia."	2C
"For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0-10.0 g/dl (90-100g/l)."	2B
Maintenance therapy	
"...we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD."	2C
"Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks."	Not graded
"...we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l)."	1A

CKD: Chronic Kidney Disease; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; LOR: level of recommendation; ND: nondialysis.

American Society of Clinical Oncology et al

Table 3 summarizes current clinical practice guidelines published jointly by the American Society of Clinical Oncology and the American Society of Hematology⁸ and from the National Comprehensive Cancer Network (v.1.2018).⁶¹



Table 3. Summary of Current Guidelines for Treatment of Anemia in Patients with Cancer

Indications	ASCO/ASH 2010 Clinical Practice Guidelines	NCCN Guidelines (v.1.2018)
ESAs are indicated for:	<ul style="list-style-type: none"> • ESAs are a recommended treatment option for patients with chemotherapy-associated anemia; RBC transfusion may also be an option • ESAs are a treatment option for patients with lower risk MDS not undergoing concurrent chemotherapy • “Although FDA label now limits the indication for ESA use to patients receiving chemotherapy for palliative intent... determining the treatment intent requires clinical judgment of an individual patient’s circumstances.” 	<ul style="list-style-type: none"> • Based on patient preference and values, patients undergoing palliative treatment or myelosuppressive chemotherapy without curative intent may be treated with ESAs using FDA-approved indications/dosing/dosing adjustments, under REMS guidelines, with informed consent of patient OR may be treated with RBC transfusions per provided guidelines • Patients with anemia due to myelosuppressive chemotherapy should be assessed for risk of adverse events due to anemia and need for initial transfusion
ESAs are NOT indicated for:	<ul style="list-style-type: none"> • Clinicians should consider other correctable causes of anemia before ESA therapy • Recommends against using ESAs to treat anemia associated with malignancy in patients (excepting those with lower risk MDS) who are not receiving concurrent myelosuppressive chemotherapy 	<ul style="list-style-type: none"> • ESA treatment is not recommended when patients are treated with myelosuppressive chemotherapy with curative intent • ESA treatment is not recommended when patients are not receiving therapy or palliative treatment, or those on non-myelosuppressive therapy
ESA treatment symptom outcomes	Evidence does not conclusively show that ESA use leads to improved quality of life as can be perceived and valued by patients; recommends that the goal of ESA use should be to avoid transfusions.	Not discussed
REMS	Notes requirement	Notes requirement
Hb levels for ESA initiation	<ul style="list-style-type: none"> • Recommended when Hb level has decreased to <10 g/dL. Whether to initiate treatment when Hb is between 10 and 12 g/dL should be determined by clinical judgment, consideration of ESA risks and benefits (transfusion 	If Hb is <11 g/dL or >2 g/dL below baseline, an evaluation for possible causes of anemia is suggested. If a cause is not identified, then anemia due to myelosuppressive chemotherapy is considered.



Indications	ASCO/ASH 2010 Clinical Practice Guidelines	NCCN Guidelines (v.1.2018)
	<p>avoidance), and patient preferences</p> <ul style="list-style-type: none"> • Transfusion is also an option 	
Span of ESA treatment	Recommends discontinuing ESA treatment when chemotherapy concludes, per FDA guidelines	Physicians advised not to administer ESAs outside the treatment period of cancer-related chemotherapy
ESA dosing modifications	<ul style="list-style-type: none"> • Recommends ESA starting doses and dose adjustments follow FDA guidelines, noting that alternative doses and schedules have not improved medical outcomes • Refers to product label directing clinicians to use the lowest possible ESA dose (ie, minimize ESA exposure) to reach the lowest Hb level sufficient to avoid RBC transfusions 	Dosing and titration directions for epoetin alfa and darbepoetin alfa are reproduced from FDA-approved labels; alternative dosing regimens are provided, eg, every 2 or 3 wk instead of weekly injections
Hb target	Hb can be raised to the lowest Hb level needed to avoid RBC transfusions. An optimal target Hb cannot be determined from the available evidence	No Hb target is mentioned; notes that the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target Hb <12 g/dL
Iron	Iron studies at baseline and periodically during treatment may be valuable to minimize the need for ESA treatment, maximize improvement of symptoms, or determine the reason for failure to respond	Iron studies and supplementation of functional iron deficiency are recommended for patients treated with ESAs. These include serum iron, TIBC, and serum ferritin. Any patient with cancer who develops a sudden loss of response to ESAs, accompanied by severe anemia and a low reticulocyte count, should be evaluated for the etiology of loss of effect.
Thromboembolic risk	Caution urged in the use of these agents with patients judged at high risk for thromboembolic events, and regarding ESA use together with therapies that increase risk of thromboembolic events	Patients with previous risk factors for thrombosis may be at higher risk when administered ESAs and should undergo risk assessment; the risk of ESA-associated thrombosis is independent of Hb levels
Response to treatment	If a patient does not respond to ESAs after 6-8 wk, despite a dose increase, ESA therapy should be discontinued, and the clinician should investigate possible underlying tumor progression, iron deficiency, or other causes of the anemia	ESA therapy should be discontinued if a patient shows no response despite iron supplementation after 8-9 wk of treatment. ESA dose-adjustment decisions are based on the goal of a gradual increase in Hb level that remains sufficient to avoid transfusion.



ASCO: American Society of Clinical Oncology; ASH: American Society of Hematology; ESA: erythropoiesis-stimulating agent; FDA: Food and Drug Administration; Hb: hemoglobin; MDS: myelodysplastic syndrome; NCCN: National Comprehensive Cancer Network; RBC: red blood cell; REMS: risk evaluation and mitigation strategy.

American Society of Nephrology

In 2012, the American Society of Nephrology released its evidence-based recommendations for the Choosing Wisely campaign to improve patient care and resource use.⁶² The Society included the following among its top 5 recommendations: “Do not administer erythropoiesis-stimulating agents to CKD patients with hemoglobin levels ≥ 10 g/dL without symptoms of anemia.”

Medicare National Coverage

In July 2007, Centers for Medicare and Medicaid Services (CMS) released a decision memorandum on the use of ESAs for nonrenal disease indications (CAG-00383N).⁹ Safety concerns such as thrombosis, cardiovascular events, tumor progression, and reduced survival, derived from clinical trials in several cancer and noncancer populations, prompted CMS to review its coverage of ESAs. Based on its review, CMS proposed conditions of coverage based on expression of erythropoietin receptors. However, the scientific understanding of this mechanism is controversial and requires additional study.

CMS also reviewed comments on ESAs for treatment of myelodysplastic syndrome (MDS), a precursor of acute myeloid leukemia (AML) in many patients. CMS retains an interest in these specific issues but does not differentiate ESA coverage by the erythropoietin receptor status of the underlying disease and has decided at this time to make no national coverage determination (NCD) on ESAs in MDS.

“CMS has determined that there is sufficient evidence to conclude that ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on the underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

- Any anemia in cancer or cancer treatment patients due to folate deficiency, vitamin B12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
- Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers



- Anemia of cancer not related to cancer treatment
- Any anemia associated only with radiotherapy
- Prophylactic use to prevent chemotherapy-induced anemia
- Prophylactic use to reduce tumor hypoxia
- Patients with erythropoietin-type resistance due to neutralizing antibodies
- Anemia due to cancer treatment if patients have uncontrolled hypertension”

CMS also determined that ESA treatment for anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma and lymphocytic leukemia is only reasonable and necessary under the following specified conditions:

- The hemoglobin (Hb) level immediately before initiation or maintenance of ESA treatment is less than 10 g/dL (or the hematocrit [Hct] is <30%).
- The starting dose for ESA treatment is the recommended FDA label starting dose (no more than 150 U/kg 3 times weekly for epoetin alfa or epoetin alfa-epbx and 2.25 mcg/kg weekly for darbepoetin alpha). Equivalent doses may be given over other approved time periods.
- Maintenance of ESA therapy is the starting dose if the Hb level remains below 10 g/dL (or Hct is <30%) 4 weeks after initiation of therapy and the rise in Hb is greater than 1 g/dL (Hct >3%).
- For patients whose Hb increases less than 1 g/dL (Hct <3%) compared with pretreatment baseline over 4 weeks of treatment and whose Hb level remains less than 10 g/dL after 4 weeks of treatment (or Hct is <30%), the recommended FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if Hb increases less than 1 g/dL (Hct <3%) compared with pretreatment baseline after 8 weeks of treatment.
- Continued administration of the drug is not reasonable and necessary if there is a rapid rise in Hb greater than 1 g/dL (Hct >3%) over 2 weeks of treatment unless Hb remains below or subsequently falls to less than 10 g/dL (Hct <30%). Continuation and reinstatement of ESA therapy must include a dose reduction of 25% from the previously administered dose.
- ESA treatment duration for each course of chemotherapy includes the 8 weeks after the last dose of myelosuppressive chemotherapy in a chemotherapy regimen.

PEG-epoetin beta is not addressed in the decision memorandum or NCD.⁶³



This decision by CMS allows local Medicare contractors to “continue to make reasonable and necessary determinations on all uses of ESAs that are not determined by NCD.”

Regulatory Status

The major regulatory timelines for approval actions for new indications are summarized next:

- Epoetin alfa (Epogen®/Procrit®):
 - 1989: Approved for use in patients with anemia due to CRF
 - 1991: Approved for use in zidovudine-treated, HIV-infected patients
 - 1993: Approved for chemotherapy-induced anemia in patients with non-myeloid malignancies
 - 1996: Approved for presurgical use in certain patients undergoing surgery
- Epoetin alfa-epbx (Retacrit™):
 - 2018: Biosimilar to Epogen®/Procrit® with the identical FDA approved indications as Epogen®/Procrit®.
- Darbepoetin alfa (Aranesp®):
 - 2001: Approved for use in patients with anemia due to CRF
 - 2002: Approved for chemotherapy-induced anemia in patients with non-myeloid malignancies
- Peginesatide (Omontys®; Takeda Pharmaceuticals, Deerfield, IL, and Affymax):
 - 2012: Approved for use in adults with anemia due to CKD who are on dialysis
 - 2013: Voluntary recall of all lots due to postmarketing reports of serious hypersensitivity
- Methoxy polyethylene glycol (PEG) epoetin-beta (Mircera®; Roche, Basel, Switzerland)
 - 2007: Approved for use in patients with anemia due to CRF who are on dialysis or not on dialysis
 - 2009: Injunction prohibiting U.S. sales until mid-2014 due to copyright infringement
 - 2015: Resumption of U.S. sales



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History

Date	Comments
12/13/11	New Policy – Add to Prescription Drug section. Policy approved with 90-day hold for



Date	Comments
	provider notification; the policy effective date is June 1, 2012.
01/10/12	Replace Policy – Conditions for medically necessary treatment updated to apply only to those patients aged 18 years and older.
04/10/12	Replace policy. Updated to allow lower iron store requirements and longer intervals between checking iron stores, specifically for patients receiving ESAs that are not receiving hemodialysis. Policy effective date remains June 1, 2012.
09/24/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
01/10/13	Coding update. HCPCS code J0890, effective 1/1/13, added to policy.
10/14/13	Replace policy. Policy updated with literature review; no change in policy statement. Repeating references removed.
02/10/14	Scope updated to indicate that this policy not part of Medicare Advantage.
04/14/14	Annual review. Policy statement updated to indicate an additional requirement of adequate B12 level (200 pg/ml) as a treatment criterion for those over 18 years of age. When treating those with chronic kidney disease, the following criteria were added: Hb level of 10 g/dL, and iron store threshold levels were differentiated for those receiving hemodialysis versus those not receiving hemodialysis, with quarterly documentation required for continued treatment. When treating cancer patients, treatment criterion include Hb level above 10 g/dL. Policy Guidelines section updated with Risk Evaluation and Mitigation Strategy (REMS) information. Peginesatide (Omontys) added to the policy as an ESA agent. Rationale and Description sections updated extensively. References removed, added and renumbered. Coding section update removing ICD-9 and ICD-10 diagnosis and procedure codes; these are not part of the adjudication of this policy.
05/12/14	Interim update. Policy statement revised: treatment initiation criterion of an adequate B12 levels (200 pg/ml) removed. This is not generally performed by the local provider community and is not considered a necessary prerequisite to treatment. Coding update: Remove HCPCS codes Q2047 and Q4081 (these are not utilized, J0881-0890 are listed on the policy and are specific to the policy).
11/10/14	Interim update. This policy is updated with a current literature review and includes the newly marketed drug pegylated (PEG) – epoetin beta.
01/05/15	Coding update. New HCPCS codes J0887 and J0888, effective 1/1/15, added to the policy.
04/14/15	Annual review. Policy section updated clarifying target Hb level ranges within the medical necessity criteria; for use in those with chronic kidney disease, adjustment made to ferritin level threshold levels; for use in cancer patients, added that documentation of iron stores is indicated only if there is no improvement in hemoglobin level with ESA use.
02/04/16	Coding update. Added Q4081.



Date	Comments
06/01/16	Annual Review, approved May 10, 2016. Policy updated with literature review through November, 2015; references added. Policy statements unchanged.
09/01/16	Interim Review, approved August 9, 2016. Added peritoneal dialysis to chronic kidney disease policy statement for clarification.
01/01/17	Interim Review, approved December 13, 2016. Clarification added to chronic kidney disease policy statement, "For ongoing ESA therapy, Hb level below 12 g/dL is considered acceptable as 11.0 to 11.9 is the target range for Hb level".
04/11/17	Policy moved into new format; no change to policy statements. Evidence Review section reformatted.
06/13/17	Coding update; removed HCPCS code J0886 as it was terminated 1/1/16.
11/01/17	Annual Review, approved October 19, 2017. Updated guidelines from KDIGO. Removed HCPCS code J0890.
03/01/18	Annual Review, approved February 27, 2018. Policy updated with literature review through August 2017; references 21-26, 44, and 46-50 added. Policy statements unchanged. Removed CPT codes 96365, 96372.
12/01/18	Interim Review, approved November 21, 2018. Added the biosimilar, Retacrit (epoetin alfa-epbx) to policy. Added HCPCS codes Q5105 and Q5106.
04/01/19	Minor update, added Documentation Requirements section.

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This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፈላጊ እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታወቅ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحتوي هذا الإشعار على معلومات مهمة بخصوص طلبك أو التخطيط التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):

Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):

Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyuog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈງການນີ້. ທ່ານອາດຈະຈໍາເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងរបស់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ដុល្លារចេញផ្លូវ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).