Erythropoiesis-Stimulating Agents (ESAs)

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor synthesized at the cellular level 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 upon 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 12–16 g/dL in women and 14–18 g/dL in men. Mild anemia is defined as Hb from 10 g/dL to the lower limit of normal ranges, while moderate anemia is 8-10 g/dL. Severe anemia is defined as Hb 8 g/dL or below.

Erythropoiesis-stimulating agents (ESAs) 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 individuals with chronic renal failure (CRF) secondary to CKD. Patients with CRF will become severely anemic, experience severe fatigue, and reduced exercise tolerance unless treated with blood transfusions or an ESA. Partial correction of anemia with ESA treatment results in reduced need for red blood cell transfusions and enhanced 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. Poor oral intake or altered metabolism may reduce nutrients (folate, iron, and vitamin B-12) essential for the red cell production. Antibodies in certain tumor types may cause increased erythrocyte destruction through hemolysis. Tumors may cause blood loss via tissue invasion, for example gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment. In more advanced cases, there may be marrow replacement with tumor or amyloid. Marrow dysfunction can occur, however, even in the absence of frank invasion. 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 red cell production. The treatment of cancer may also cause anemia. Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells.
Erythropoiesis-Stimulating Agents (ESAs)

Red blood cell (RBC) transfusion is the traditional approach to quickly ameliorate anemia symptoms. However, it is not risk free, with several potential associated adverse events. The highest adverse event risk (1 per 432 whole blood units) is that for transfusion-related acute lung injury (TRALI). Adverse events due to errors in transfusion (for example, type mismatch) are estimated to occur at a rate of 1 per 5,000–10,000 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), human immunodeficiency virus (HIV) (<1 in 1,000,000), and bacterial contaminants (1 per 10,000-100,000) have fallen dramatically since the early 1990s. Therefore, while the initial impetus for commercialization of erythropoietin replacement products was based on reduction in the risks associated with blood transfusion, current practices have mitigated many of those. Nonetheless, blood shortages, transfusion errors, and the risk for alloimmunization and TRALI provide sufficient rationale for the use of ESA therapy in appropriately indicated patients.

Four ESA products have been licensed in the U.S. 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 Ortho Biotech, LP, a subsidiary of Johnson and Johnson, under the proprietary name, Procrit®. Under a contractual agreement with Amgen, Ortho Biotech LP has rights to development and marketing of Procrit® for any indication other than for the treatment of anemia associated with chronic renal failure in patients on dialysis or use in diagnostic test kits. Epogen and Procrit have identical labeling information for all U.S. Food and Drug Administration (FDA) -approved indications. A second ESA, darbepoetin alfa, is marketed by Amgen solely under the proprietary name, Aranesp®. The third ESA product, peginesatide, was co-developed and commercialized by Affymax, Inc. and Takeda Pharmaceuticals, who market it under the proprietary name, Omontys®. In February 2013, Affymax, Takeda, and FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. 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 the brand name Mircera®. Mircera sales in the US 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.

The epoetin alfas and epoetin beta have the same amino acid sequence as endogenous erythropoietin, but differ from each other in glycosylation; clinical effects are considered interchangeable. Darbepoetin alfa has 2 additional oligosaccharide chains. In contrast, peginesatide lacks any amino acid sequence homology to erythropoietin. It is a synthetic dimer of identical 21-amino acid peptides bound to a linker and to polyethylene glycol, with a total molecular weight of approximately 45,000 daltons. However, the epoetins, darbepoetin, and peginesatide all have pharmacologic actions similar to those of the endogenous hormone. Each binds to and activates the human erythropoietin receptor and thus increases the number of red blood cells and the blood concentration of hemoglobin, when given to individuals with functioning erythropoiesis. Both epoetin alfas, PEG-epoetin beta and darbepoetin are FDA approved to treat anemia associated with CKD in patients on dialysis or not on dialysis. Peginesatide is approved only for adult patients with anemia from CKD who are on dialysis. Epoetin alfa and darbepoetin also are approved for other indications.

Regulatory Status
The major regulatory time line for approval actions pertaining to new indications is summarized below:
Erythropoiesis-Stimulating Agents (ESAs)

**Epoetin alfa (Epogen/Procrit):**
- 1989: approved for use among anemic CRF patients
- 1991: approved for use among zidovudine-treated HIV-infected patients
- 1993: approved for use among chemotherapy-induced anemia in patients with non-myeloid malignancies
- 1996: approved for presurgical use among certain patients undergoing surgery

**Darbepoetin alfa (Aranesp):**
- 2001: approved for use among anemic CRF patients
- 2002: approved for use among chemotherapy-induced anemia in patients with non-myeloid malignancies

**Peginesatide (Omontys):**
- 2012: approved for use among anemic adults with CKD on dialysis
- 2013: Voluntary recall of all lots due to postmarketing reports of serious hypersensitivity

**Methoxy polyethylene glycol (PEG) epoetin-beta (Mircera®):**
- 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

On November 8, 2007, the FDA revised the product labeling for epoetin alfa and darbepoetin alfa. These revisions clarified the evidence for safety and effectiveness of these products and provided more explicit directions and recommendations for their use. These recommendations were consistent with those made during the May 10, 2007 ODAC and the September 11, 2007 CRDAC and DSRMAC meetings. Revisions included strengthened **boxed warnings and “Warnings and Precautions”** sections, and changes to the “Indications and Usage,” “Clinical Trials Experience,” and “Dosage and Administration” sections of the product labels. Product labels for Epogen/Procrit and Aranesp have been revised many times since then. The revised black box warnings and limitations of use shown next reflect current labeling for these ESAs. Although the Mircera product label has not been updated since 2007, “Warnings” for use in CRF are similar to those listed next.

**Cancer**
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non–small cell lung, head and neck, lymphoid, and cervical cancers.
- Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense an ESA to patients with cancer.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue use after the completion of a chemotherapy course.

**Chronic Renal Failure**
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target an Hb level of greater than 11 g/dL.
- No trial has identified an Hb target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Epogen/Procrit or Aranesp dose sufficient to reduce the need for RBC transfusions.
Erythropoiesis-Stimulating Agents (ESAs)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for erythropoiesis stimulating agents (ESAs) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member’s Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Erythropoiesis-Stimulating Agents (ESAs) are covered

The use of epoetin alfa, darbepoetin, or pegylated (PEG)-epoetin beta may be considered medically necessary for:

1. Treatment of anemia associated with chronic kidney disease if:
   a) The patient is on dialysis with a hemoglobin of <10 g/dL (in the last 4 weeks); OR
   b) The patient is not on dialysis with a hemoglobin of <10 g/dL (in the last 4 weeks) and is steadily decreasing, indicating a high likelihood for RBC transfusion.

2. Treatment of anemia due to myelodysplastic syndrome if:
   a) The patient’s hemoglobin is <12 g/dL when starting ESA therapy; OR
   b) The patient’s hemoglobin is ≤12 g/dL while receiving and stable on ESA therapy.

3. Treatment for reduction of allogenic blood transfusions if:
   a) The patient is a surgical patient; AND
   b) The patient’s hemoglobin is >10 g/dL and ≤13 g/dL.

4. Treatment for anemia due to myelosuppressive and chemotherapy if:
   a) The patient has non-myeloid malignancy; AND
   b) The patient’s hemoglobin is <10 g/dL (in the last 4 weeks); AND
   c) The patient is currently on or has been received chemotherapy in the last 6 months; AND
   d) Chemotherapy is not intended to be curative; AND
   e) Mircera is not the intended ESA agent for therapy.

5. Treatment for anemia related to zidovudine treatment if:
   a) The patient has been diagnosed with HIV/AIDS; AND
   b) The patient is being treated with zidovudine; AND
   c) The patient’s hemoglobin is <12 g/dL when starting ESA therapy; OR
   d) The patient’s hemoglobin is ≤12 g/dL while receiving and stable on ESA therapy.

6. Other indications if:
   a) The patient’s hemoglobin is <12 g/dL when starting ESA therapy; OR
   b) The patient’s hemoglobin is ≤12 g/dL while receiving and stable on ESA therapy; AND
   c) The prescriber has submitted documentation in support of the use of the prescribed ESA for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist.
Erythropoiesis-Stimulating Agents (ESAs)

Use of Erythropoiesis Stimulating Agents (ESAs) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

FDA-approved label for epoetin alfa (Epogen®, Procrit®)
FDA-approved label for darbepoetin alfa (Aranesp®)
FDA-approved label for PEG-epoetin beta (Mircera®)

When Erythropoiesis-Stimulating Agents (ESAs) are not covered

The use of epoetin alfa or darbepoetin is considered *investigational* for:

- treatment of patients following high-dose chemotherapy with autologous stem-cell support;
- treatment of non-iatrogenic chronic anemia of cancer;
- other cancer-associated anemia excepted as noted above.

Erythropoiesis Stimulating Agents (ESAs) are considered investigational when used for:

1. Non-cancer indications; OR
2. When criteria are not met regarding FDA labelling OR strong endorsement/support by nationally recognized compendia, as stated under “When Erythropoiesis Stimulating Agents (ESAs) are covered.”

Policy Guidelines

Administration

Erythropoiesis-stimulating agents (ESAs) and pegylated (PEG) epoetin beta are to be administered according to current Food and Drug Administration (FDA) approved labeling for each product, using recommended hemoglobin (Hb) levels for starting, stopping, and dose adjustment. This includes decreasing the dose of ESA as the Hb approaches the target level.

Before starting 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

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.
Erythropoiesis-Stimulating Agents (ESAs)

ESAs and PEG-Epoetin Beta

Patients with chronic kidney disease who do not respond adequately over a 12-week dose escalation period should not have their ESA or PEG-eoetin beta dose increased further. Increasing ESA or PEG-eoetin beta dose further is unlikely to improve response and may increase risks; the lowest ESA or PEG-eoetin beta dose that maintains adequate 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-eoetin beta therapy.

Risk Evaluation and Mitigation Strategy

Epoetin alfa and darbepoeitin must be prescribed and dispensed in accordance with a risk evaluation and mitigation strategy (REMS) drafted by the manufacturer and approved by FDA.

REMS for epoetin alfa and darbepoeitin alfa each comprise elements to assure safe use and an implementation system.

- ESA manufacturers must ensure that all hospitals and healthcare professionals who prescribe and/or dispense ESAs to patients with cancer have enrolled and completed training in the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program. The ESA APPRISE program began on March 24, 2010 after FDA’s initial approval of separate but similar REMS for epoetin alfa and darbepoeitin alfa on February 16, 2010. Both REMS were subsequently modified, most recently on December 31, 2013.

- Healthcare providers and hospitals that prescribe and/or dispense an ESA for chronic kidney disease (CKD) must provide each patient with a copy of the REMS Medication Guide included in the product label and ensure that patients are adequately informed of the risks associated with ESA treatment. However, prescribers are not required to enroll in and complete the ESA APPRISE program.

PEG-eoetin beta does not have a REMS.

On March 27, 2012, FDA approved a REMS for peginesatide with a communication plan as its only component. The plan’s goal was to inform all healthcare professionals who might prescribe the drug that peginesatide is indicated only for adult patients with CKD on dialysis, and of potentially fatal risks associated with its use in CKD patients not on dialysis. Peginesatide is currently discontinued.

Endogenous erythropoietin (EPO) is a glycoprotein hematopoietic growth factor that regulates hemoglobin levels in response to changes in the blood oxygen concentration. Erythropoiesis-stimulating agents (ESAs) are produced using recombinant DNA technologies and have pharmacologic properties similar to endogenous EPO. The primary clinical use of ESAs is in patients with chronic anemia.

The evidence for erythropoiesis-stimulating agents (ESAs) in individuals who have chronic kidney disease and anemia 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, including epoetin alfa, darbepoeitin, and PEG-eoetin beta, have been studied and approved for this use. Most of the evidence has demonstrated a decrease in the need for blood transfusions but has failed to demonstrate any significant improvement in other clinical outcomes, including mortality, morbidity, functional status, or quality of life. Many studies have, in fact, demonstrated increased mortality risk and increased risk for venous access thrombosis and stroke, prompting FDA warnings and a REMS. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for erythropoiesis-stimulating agents (ESAs) in individuals who have anemia secondary to cancer (or its treatment) includes RCTs and systematic reviews of RCTs. Relevant outcomes are
Erythropoiesis-Stimulating Agents (ESAs)

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. Epoetin alfa and darbepoetin are the ESAs approved for use in treatment of cancer-related anemia; PEG-epoetin beta is not FDA approved for this indication, as 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.

The evidence for erythropoiesis-stimulating agents (ESAs) in individuals who have hepatitis C treated with ribavirin includes RCTs. Relevant outcomes are medication use and quality of life. Evidence from RCTs demonstrates that treatment with ESAs improves the ability to maintain full-dosing of ribavirin, as 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 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.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J0881, J0882, J0885, J0886, J0887, J0888, S0353, S0354, Q4081

ICD-10 Codes: C00.0-C49.9, C4A.0-C4A.9, C50.011-C79.9, C7A.00-C7A.8, C7B.00-C7B.8, C80.0-C86.6, C88.2-C96.Z, D00.00-D09.9, Z51.11, Z51.12

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director 8/2011


Specialty Matched Consultant Advisory Panel review 3/20/2013
Erythropoiesis-Stimulating Agents (ESAs)


Medical Director review 3/2015


Medical Director review 9/2016


Policy Implementation/Update Information

8/30/11 New Guideline implemented. ESA may be appropriate for: treatment of anemia associated with chronic kidney disease; treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy; treatment of anemia related to therapy with AZT (zidovudine) in HIV-infected patients; reduction of allogeneic blood transfusion in surgery patients; treatment of patients following allogeneic bone marrow transplantation; and treatment of patients with myelodysplastic syndromes to reduce transfusion dependency. Medical Director review 8/6/2011. (btw)

2/12/13 Information regarding Peginesatide (Omontys®) added to Description section. Under Evidence Based Guideline added; “The use of an ESA may be appropriate for treatment of patients with hepatitis C and anemia related to ribavirin treatment.” “The use of peginesatide may be appropriate for: treatment of anemia associated with chronic kidney disease in adults on dialysis.” Medical Director review 1/15/2013. Reference added. (btw)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No change to evidence based guideline. (btw)

2/11/14 Added the following statement to the Description section; “In February 2013, Affymax, Takeda, and FDA announced a voluntary recall of all lots of peginesatide due to postmarketing reports of serious hypersensitivity reactions, including anaphylaxis. FDA currently lists peginesatide (Omontys) as discontinued.” Removed “The use of peginesatide may be appropriate for: treatment of anemia associated with chronic kidney
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disease in adults on dialysis.” from the Evidence Based Guideline section. Reference added. (btw)


10/28/14 Minor updates to the “Description section.” Added the statement: “The use of PEG-epoetin beta is not recommended for all other indications” to the Not Recommended section. Reference added. (lpr) 12/30/14 Added HCPCS codes J0887 and J0888 to Billing/Coding section for effective date 1/1/2015. (lpr)

7/28/15 Evidence based guideline converted to corporate medical policy. Medical Director review. Specialty matched consultant advisory panel review meeting 3/25/2015. Notification given 7/28/15 for effective date 10/1/15. (lpr)

10/1/15 Under “When Covered” section: reversed the order of statement “For medically necessary use in cancer patients, these additional FDA criteria should be considered: ESA therapy should not be initiated at Hb levels ≥10 g/dL and ESA treatment should be discontinued following the completion of a myelosuppressive chemotherapy course” with the statement “In the medically necessary conditions noted above, the following criteria should be considered: the lowest dose of ESAs should be used in order to avoid red blood cell transfusions; ESAs should not be used to raise the Hb level above 12g/dL; and ESA therapy should not be administered without adequate iron stores.” No change to policy statement. (lpr)

4/29/16 Updated Policy Guidelines and Description sections. Reference added. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

12/30/16 Updated Policy Guidelines section. Added covered indication language to “When Covered” section.” Updated Regulatory status section with black box warning. ICD-10 diagnoses codes and S0353, S0354 added to “Billing/Coding” section. Senior Medical Director review 9/2016. Notification given 12/30/16 for effective date 4/1/17. (lpr)

4/28/17 Added the following statement to “When Covered” section: “Use of Erythropoiesis Stimulating Agents (ESAs) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached”. Under “When Not Covered” section, added the statement “Erythropoiesis Stimulating Agents (ESAs) are considered investigational when used for: 1)Non-cancer indications; OR 2) When criteria are not met regarding FDA labeling OR strong endorsement/ support by nationally recognized compendia, as stated under “When Erythropoiesis Stimulating Agents (ESAs) are covered.” Added the following statements under “Policy Guidelines” section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Medical Director review 3/2017. Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment
Erythropoiesis-Stimulating Agents (ESAs)

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review
and revise its medical policies periodically.