

## Corporate Medical Policy

### Interleukin-5 Antagonists

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<b>Origination:</b>	2/2016
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#### Description of Procedure or Service

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##### **Mepolizumab (Nucala®)**

Mepolizumab (Nucala) is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. It is also indicated in the treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss Syndrome). Mepolizumab (Nucala) is not indicated for treatment of other eosinophilic conditions, for relief of acute bronchospasm or for status asthmaticus.

Mepolizumab (Nucala) is an interleukin-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma has not been definitively established.

##### **Reslizumab (Cinqair®)**

Reslizumab (Cinqair) is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype. Reslizumab (Cinqair) is not indicated for treatment of other eosinophilic conditions, for relief of acute bronchospasm or for status asthmaticus.

Reslizumab (Cinqair) is an interleukin-5 antagonist (IgG4 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Reslizumab (Cinqair) binds to IL-5 with a dissociation constant of 81 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Reslizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of reslizumab action in asthma has not been definitively established.

##### **Benralizumab (Fasenra™)**

Benralizumab (Fasenra) is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Benralizumab (Fasenra) is

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not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

Benralizumab (Fasenra) is an interleukin-5 antagonist (IgG1 kappa) that binds directly to the alpha subunit of the human IL-5 receptor on an eosinophil with a dissociation constant of 11pM, and works to uniquely attract natural killer cells to induce apoptosis (programmed cell death). Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Benralizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of benralizumab action in asthma has not been definitively established.

**\*\*\*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

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**BCBSNC will provide coverage for interleukin-5 antagonists when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

## Benefits Application

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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 Interleukin-5 Antagonists are covered

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### Initial Coverage Review:

Interleukin-5 Antagonists are considered medically necessary for the treatment of severe eosinophilic asthma when the following criteria are met:

1. For Mepolizumab (Nucala) and Benralizumab (Fasenra) the individual is 12 years of age or older; for Reslizumab (Cinqair) the individual is 18 years of age or older; **AND**
2. Symptoms are inadequately controlled with use of either combination therapy:
  - a. 12 months of high-dose inhaled corticosteroid (ICS) given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist [LABA], or leukotriene receptor antagonist [LTRA], or theophylline), unless the individual is intolerant of, or has a medical contraindication to these agents;  
**OR**
  - b. 6 months of ICS with daily oral glucocorticoids given in combination with a minimum of 3 months of controller medication (either a LABA, or LTRA, or theophylline), unless the individual is intolerant of, or has a medical contraindication to these agents; **AND**
3. Has one of the following blood eosinophil counts (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection):
  - a. Greater than or equal to 150 cells/microliter\* at initiation of therapy for mepolizumab and benralizumab, and greater than 400 cells/microliter for reslizumab;  
**OR**

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- b. Greater than or equal to 300 cells/microliter\* for mepolizumab and benralizumab, and greater than 400 cells/microliter for reslizumab in the prior 12 months;

\*Note: 1 microliter (ul) is equal to 1 cubic millimeter (mm<sup>3</sup>)

**AND**

4. Diagnosis of asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids.

Mepolizumab (Nucala) is considered medically necessary for adults aged 18 years or older who are diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss Syndrome) for 6 months or greater, and who are stable on oral corticosteroids (OCS).

### **Continuation of therapy after 12 months:**

Continued therapy after 12 months is considered medically necessary for the treatment of an individual with documented severe eosinophilic asthma when clinical improvement has been demonstrated by one or more of the following:

- Decreased utilization of rescue medications; **OR**
- Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in ICS dose or treatment with systemic corticosteroids); **OR**
- Increase in predicted FEV1 from pretreatment baseline; **OR**
- Reduction in reported asthma-related symptoms, such as, asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.

### **When Interleukin-5 Antagonists are not covered**

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**Interleukin-5 antagonists** are considered investigational and not medically necessary when the above criteria are not met and for all other conditions, including but not limited to:

- aspirin-exacerbated respiratory disease (AERD)
- atopic dermatitis
- eosinophilic esophagitis
- nasal polyposis
- hypereosinophilic syndromes (other than severe eosinophilic asthma)
- acute bronchospasm
- status asthmaticus
- diagnosis of any non-FDA approved indication (including urticaria and other eosinophilic conditions)
- Benralizumab is not approved at 2mg, 20mg, 100mg doses.

### **Policy Guidelines**

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#### **Mepolizumab (Nucala®)**

On November 4, 2015, the U.S. Food and Drug Administration approved Mepolizumab (Nucala) for use with other asthma medicines for the maintenance treatment of asthma in patients age 12 years and older. Mepolizumab (Nucala) is approved for patients who have a history of severe asthma attacks (exacerbations) despite receiving their current asthma medicines.

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Mepolizumab (Nucala) is administered once every four weeks by subcutaneous injection by a health care professional into the upper arm, thigh, or abdomen, with prescribed dosing not to exceed 100 mg every 28 days. Mepolizumab (Nucala) is a humanized interleukin-5 antagonist monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cells. Mepolizumab reduces severe asthma attacks by reducing the levels of blood eosinophils, a type of white blood cell that contributes to the development of asthma.

The safety and efficacy of Mepolizumab (Nucala) were established in three double-blind, randomized, placebo-controlled trials in patients with severe asthma on currently available therapies. Mepolizumab (Nucala) or a placebo was administered to patients every four weeks as an add-on asthma treatment. Compared with placebo, patients with severe asthma receiving Mepolizumab had fewer exacerbations requiring hospitalization and/or emergency department visits, and a longer time to the first exacerbation. In addition, patients with severe asthma receiving Mepolizumab experienced greater reductions in their daily maintenance oral corticosteroid dose, while maintaining asthma control compared with patients receiving placebo. Treatment with mepolizumab did not result in a significant improvement in lung function, as measured by the volume of air exhaled by patients in one second.

On December 12, 2017, the U.S Food and Drug Administration approved mepolizumab (Nucala) for use in individuals 18 years or older with EGPA, previously known as Churg-Strauss syndrome. The recommended dosage of mepolizumab for the treatment of EGPA is 300mg administered once every 4 weeks by subcutaneous injection as three separate 100mg injections.

The safety and efficacy of mepolizumab was evaluated in a 52-week multicenter, parallel-group, double-blind, phase III trial of adults who had received 300mg of mepolizumab (Nucala) or placebo administered subcutaneously once every four weeks, while continuing on a stable prednisolone or prednisone dose OCS therapy. Starting at week four, OCS was tapered during the treatment period. The primary efficacy assessment in the trial measured treatment impact of Nucala on disease remission (i.e., becoming symptom free) while on an OCS dose less than or equal to 4 mg of prednisone or  $\leq 7.5$ mg of prednisolone. Remission was defined as a Birmingham Vasculitis Activity Score (BVAS), version 3, of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity). Patients receiving 300mg of Nucala achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of patients receiving 300mg of Nucala achieved remission at both week 36 and week 48 compared with placebo. In addition, significantly more patients who received 300mg of Nucala achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with patients who received the placebo.

Mepolizumab is being investigated for use in the treatment of other conditions, including but not limited to, aspirin-exacerbated respiratory disease (AERD), eosinophilic esophagitis (EoE), and hypereosinophilic syndromes (HES) unresponsive to other treatments. To date, the FDA has not approved mepolizumab for the treatment of any of these conditions.

### **Reslizumab (Cinqair®)**

On March 28, 2016, the U.S. Food and Drug Administration approved reslizumab (Cinqair) for use with other asthma medicines for the maintenance treatment of asthma in patients age 18 years and older. Reslizumab (Cinqair) is approved for patients who have a history of severe asthma attacks (exacerbations) despite receiving their current asthma medicines.

Reslizumab (Cinqair) prescribed dosing of 3mg/kg is administered once every four weeks by intravenous infusion in a clinical setting prepared to manage anaphylaxis. Reslizumab (Cinqair) is a humanized interleukin-5 antagonist monoclonal antibody produced by recombinant DNA technology in murine myeloma non-secreting 0 (NS0) cells. Reslizumab (Cinqair) reduces severe asthma attacks by reducing the levels of blood eosinophils, a type of white blood cell that contributes to the development of asthma.

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The safety and efficacy of Reslizumab (Cinqair) were established in four double-blind, randomized, placebo-controlled trials in patients with severe asthma on currently available therapies. Cinqair or a placebo was administered to patients every four weeks as an add-on asthma treatment. Compared with placebo, patients with severe asthma receiving Reslizumab (Cinqair) had fewer asthma attacks, and a longer time to the first attack. In addition, treatment with Reslizumab (Cinqair) resulted in a significant improvement in lung function, as measured by the volume of air exhaled by patients in one second.

### **Benralizumab (Fasenra™)**

On November 14, 2017, the U.S Food and Drug Administration approved benralizumab (Fasenra) for the add-on maintenance treatment of patients with severe asthma age 12 years and older, and with an eosinophilic phenotype.

Benralizumab (Fasenra) prescribed dosing is 30mg administered subcutaneously once every four weeks for the first 3 doses, and then once every eight weeks thereafter. Fasenra is for subcutaneous use only and should be administered in a clinical setting prepared to manage anaphylaxis. Benralizumab (Fasenra) is a humanized interleukin-5 antagonist monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cells. Benralizumab binds directly to the alpha subunit of the IL-5R $\alpha$  which is expressed on the surface of the eosinophils and basophils. In vitro setting, the absence of fucose in the Fc domain of benralizumab facilitates binding (45.5 nM) to Fc $\gamma$ RIII receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC).

The safety and efficacy of Benralizumab (Fasenra) were established in one 52-week dose-ranging trial, three confirmatory trials, and one 12-week lung function trial. Results from the dose-ranging trial including exposure-response modelling of exacerbation rate reduction supported the evaluation of benralizumab 30mg in the subsequent trials. Trial 1 and 2, were randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials in patients 12 years of age and older and 48 and 56 weeks in duration, respectively. The clinical development for Benralizumab is based on the 12-week, randomized, double-blind, placebo-controlled lung function trial conducted in 211 patient with mild to moderate asthma. Patients were treated with placebo or benralizumab 30mg SC every 4 weeks for 3 doses. Lung function, as measured by the change from baseline in FEV1 at Week 12 was improved in the benralizumab treatment group compared to placebo.

### **Interleukin-5 Antagonist Therapy with Mepolizumab (Nucala) or Reslizumab (Cinqair)- Site of Care Eligibility**

1. Interleukin-5 Antagonist Therapy with either Mepolizumab (Nucala) or Reslizumab (Cinqair) administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of Mepolizumab (Nucala) or Reslizumab (Cinqair) infusion is not medically necessary.
2. Mepolizumab (Nucala) or Reslizumab (Cinqair) administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
  - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
  - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
  - c. First infusion, OR
  - d. Less than 3 months since first Mepolizumab (Nucala) or Reslizumab (Cinqair) infusion, OR
  - e. First infusion after six months of no Mepolizumab (Nucala) or Reslizumab (Cinqair) infusions, OR
  - f. Requirement of a change in Interleukin-5 Antagonist product.
3. Members who do not meet the criteria above are appropriate for Interleukin-5 Antagonist Therapy with either Nucala or Cinqair administration in a **home-based** or physician office

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setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

## **Billing/Coding/Physician Documentation Information**

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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](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: C9399, J0517, J2182, J2786, J3490, J3590*

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**

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### **For Policy titled, “Mepolizumab (Nucala®)”**

Mepolizumab (Nucala®) Prescribing Information. Accessed on January 7, 2016 from [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/103976s5102lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf) American Academy of Allergy Asthma and Immunology (AAAAI). Practice Parameters: Allergy Diagnostic Testing. Available at: <http://www.aaaai.org>. Accessed on January 7, 2016.

FDA approves Nucala to treat severe asthma [news release]. Silver Spring, MD U.S. Food and Drug Administration November 4, 2015. Accessed on January 7, 2016 from: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm471031.htm>.

Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol.* 2011; 128:989-995, e1-e8.

Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010; 125(6):1336-1343.

Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol.* 2013; 131:461.

Otani IM, Anilkumar AA, Newbury RO, et al. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2013; 131(6):1576-1582.

Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy.* 2005; 60:693.

Specialty Matched Consultant Advisory Panel review 2/2016

Senior Medical Director review 2/2016

### **For Policy titled, “Interleukin-5 Antagonists”**

FDA approves Reslizumab (Cinqair) to treat severe asthma [news release]. Silver Spring, MD U.S. Food and Drug Administration March 23, 2016. Accessed on April 8, 2016 from:

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<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491980.htm>

Reslizumab (Cinqair) Prescribing Information. Accessed on March 28, 2016 from [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/761033lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf)

Specialty Matched Consultant Advisory Panel review 11/2016

Medical Director review 11/2016

Fasenra (benralizumab) received US FDA approval for severe eosinophilic asthma. November 17, 2017. AstraZeneca.

<https://www.astrazeneca.com/media-centre/press-releases/2017/fasenra-benralizumab-receives-us-fda-approval-for-severe-uncontrolled-eosinophilic-asthma-14112017.html>

Benralizumab (Fasenra) Prescribing Information. Accessed January 3, 2018.

FitzGerald, Mark J., Bleecker, Eugene R., et al. Benralizumab, an anti-interleukin-5 receptor  $\alpha$  monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3. *The Lancet*. October 29, 2016; Vol. 388, No. 10056.

Bleecker, Eugene R. FitzGerald, Mark J., et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting  $\beta^2$ -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *The Lancet*, October 29, 2016; Vol. 388, No. 10056, pp.2115-2127.

FDA approves first drug for Eosinophilic Granulomatosis with Polyangiitis, a rare disease formerly known as the Churg-Strauss Syndrome [news release]. Silver Spring, MD U.S. Food and Drug Administration December 12, 2017. Accessed from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm588594.htm>

Wechsler ME, MD, Akuthota P, MD, Jayne D, MD, et al. EGPA Mepolizumab Study Team. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. May 2017;376(20):1921-1932.

Medical Director review 2/2018

Specialty Matched Consultant Advisory Panel review 11/2018

## Policy Implementation/Update Information

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2/29/16 Original policy issued titled, “Mepolizumab (Nucala®)” with the following policy statement, “BCBSNC will provide coverage for Mepolizumab (Nucala®) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.” Specialty Matched Consultant Advisory Panel review 2/2016. Senior Medical Director review 2/2016. (td)

4/29/16 **Policy title changed from “Mepolizumab (Nucala®)” to “Interleukin-5 Antagonist”**. Policy revised to include information and criteria regarding Reslizumab (Cinqair). References updated. Medical Director review on 4/2016. (jd)

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- 9/30/16 Moved dosing information for Nucala and Cinqair from the “When Covered” section to the Policy Guidelines. Under “Billing/Coding” section, deleted code C3999 and added code C9481 for effective date 10/1/16. (jd)
- 12/30/16 Code section updated. Specialty Matched Consultant Advisory Panel review 11/2016. Medical Director review 11/2016. (jd)
- 12/29/17 Policy Guidelines updated to include guidelines for “Site of Care Eligibility” related to infusion for Mepolizumab (Nucala) or Reslizumab (Cinqair). Specialty Matched Consultant Advisory Panel review 11/2017. Medical Director review 11/2017. Policy notification given 12/29/17 for effective date 4/1/18. (jd)
- 1/26/18 Policy revised to include information and criteria regarding Benralizumab (Fasenra). When Covered section revised to include medically necessary criteria for benralizumab under items #1 and #3. When Not Covered section revised, adding last bullet item: “Benralizumab is not approved at 2mg, 20mg, 100mg doses.” Added codes J3490, J3590 and C9399 to Coding section. References updated. Notification given for PPA for codes J3490, J3590 and C9399, with effective date 4/1/18. Specialty Matched Consultant review 1/2018. (jd)
- 2/23/18 Policy revised to include new FDA approval of Mepolizumab (Nucala) for eosinophilic granulomatosis polyangiitis (EGPA). Description section updated. Added item 5 to When Covered section: “Treatment with mepolizumab (Nucala) is considered medically necessary for adults (18 years or older) diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss Syndrome) for 6 months or greater, and stable on oral corticosteroids (OCS).”. Policy Guidelines and reference section updated. Policy remains on notice for Benralizumab and codes J3490, J3590 and C9399, effective 4/1/18. Medical Director review 2/2018. (jd)
- 5/25/18 Code C9466 added to Billing/Coding section. (krc)
- 12/14/18 Minor changes made to Description and Policy Guidelines sections for clarity. Minor edits and formatting changes made to policy statement for clarity. No change to policy intent. Specialty Matched Consultant Advisory Panel review 11/28/2018. (krc)
- 12/31/18 Added HCPCS code J0517 to Billing/Coding section and deleted code C9466 effective 1/1/19. (krc)

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