PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/20/2021
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BRONCHITOL® (mannitol)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Bronchitol (mannitol) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of cystic fibrosis
  4. Will be used as add-on maintenance therapy to improve pulmonary function
  5. Individual will continue their other cystic fibrosis therapies
  6. Individual has a prescription for short-acting bronchodilator therapy to use with each dose of Bronchitol (mannitol)
  7. Individual does not have a history of hemoptysis (episode of 60 ml or more) within the previous 3-months
  8. Individual has failure, contraindication or intolerance to **ALL** of the following agents:
     a. Inhaled Pulmozyme (dornase alpha)
     b. Inhaled hypertonic (7%) saline
  9. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Individual has taken and passed the Bronchitol Tolerance Test
     b. Individual has a baseline FEV1 between 40% and 90% predicted
  10. There are **NO** contraindications. Contraindications include:
      a. Failure to pass the Bronchitol Tolerance Test
      b. Hypersensitivity to mannitol

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Bronchitol (mannitol) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist
  2. Individual's condition responded while on therapy.
     a. Response is defined as **ONE** of the following:
        i. There is documentation of improvement in FEV1 over baseline of at least 100 mL
        ii. There is documentation of improvement in FEV1 over baseline of at least 10%

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Severe bronchospasms
        ii. Hemoptysis

5. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of a Non-Cancer Medications**

    2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Bronchitol (mannitol) is indicated as add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with cystic fibrosis (CF). Use Bronchitol (mannitol) only for adults who have passed the Bronchitol Tolerance Test (BTT). The BTT must be administered and performed under the supervision of a healthcare practitioner who is able to manage acute bronchospasm, to identify patients who are suitable candidates for Bronchitol (mannitol) maintenance therapy.

An individual who experiences any of the following: bronchospasm, a decrease in FEV1, or a decrease in oxygen saturation with administration of Bronchitol (mannitol) is deemed to have failed the BTT. Bronchitol (mannitol) must not be prescribed. Individual who passes the BTT is a candidate for Bronchitol (mannitol) and must have inhaled short-acting bronchodilator therapy before each use of Bronchitol (mannitol).

Difficulty clearing purulent secretions from the airways is a common complaint among CF patients who have moderate to severe lung disease. Airway clearance is accomplished by a combination of inhaled drugs such as dornase alfa and/or hypertonic saline to loosen and liquefy the mucus along with physical means to dislodge and help the patient clear the secretions. It has been shown that dornase alfa reduces pulmonary exacerbations and improves lung function. Regular treatment with hypertonic saline leads to only modest improvements in lung function in adults and children, but there are substantial reductions in pulmonary exacerbations. There is little evidence that N-acetylcysteine has any beneficial effect. Use of inhaled N-acetylcysteine is no longer recommended within the guidance from the Cystic Fibrosis Foundation (CFF). This agent can liquefy CF sputum, but it has the potential to induce airway inflammation and/or bronchospasm in a subgroup of patients and to inhibit ciliary function which has led to a reduction in its use.

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In a published guideline in 2013 the CFF supported the use of inhaled dornase alpha to improve lung function and reduce exacerbations for individuals 6-years of age and older with mild disease and for individuals 6-years of age and older with moderate to severe disease. It also supported the use of inhaled hypertonic saline in individuals 6-years of age and older to improve lung function, quality of life, and reduce exacerbations. Severity of lung disease was defined by FEV1% predicted as follows: normal, > 90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, < 40% predicted. The CFF recommended the following order of inhaled medications: bronchodilator; hypertonic saline; dornase alfa; airway clearance; and aerosolized antibiotic.

Dornase alfa is an endonuclease that decreases the viscosity of purulent CF sputum by cleaving long strands of denatured DNA that are released by degenerating neutrophils, which helps to liquefy CF sputum. Inhaled hypertonic saline or inhaled mannitol helps to hydrate the mucus that is present in the airways of patients with CF. Guidelines from the CFF recommend that most patients with CF use both dornase alfa and hypertonic saline, without assigning priority of one over the other. Inhaled mannitol is considered a second-line option to replace hypertonic saline for adult patients with CF who fail the combination of dornase alfa and hypertonic saline for airway clearance.

In 2020 a Cochrane Database Systematic Review of inhaled mannitol indicated that moderate-quality evidence showed that treatment with mannitol over a six-month period was associated with an improvement in some measures of lung function in people with CF compared to various controls (very low dose of mannitol, non-respirable mannitol, and dornase alpha). It also concluded that mannitol could be considered as a treatment in CF; but further research is required in order to establish who may benefit most and whether this benefit is sustained in the longer term. The review noted that studies comparing its efficacy against other (established) mucolytic therapies need to be undertaken before it can be considered for mainstream practice.

All patients should have an airway clearance regimen with the following: 1) children of any age who have chronic daily cough or FEV1 below the normal range, chronic treatment with dornase alfa is recommended. It is also recommended that dornase alfa treatment be used for patients with mild or asymptomatic lung disease. 2) chronic treatment with inhaled hypertonic saline for patients ≥ 2 years is also recommended. It is also suggested as therapy for younger children and infants. Typical dosing regimen is 4 mL of 7% saline via nebulizer twice daily. Because inhaled hypertonic saline can trigger acute bronchospasm, bronchodilator therapy (e.g., with a short-acting beta-adrenergic agonist) is given as a pretreatment. 3) all patients who produce sputum should be encouraged to adhere to a regular regimen of chest physiotherapy for secretion clearance. 4) respiratory therapies should be performed twice daily in the following order: inhaled short-acting beta-adrenergic agonist, then inhaled hypertonic saline, then inhaled dornase alfa (given only once daily) and chest physiotherapy in either order, followed by any other inhaled treatments such as aerosolized antibiotics.

Resources:

Bronchitol (mannitol) product information, revised by Chiesi USA, Inc. 19-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed February 10, 2021.

Jones PW, Beeh KM, Chapman KR, et al.: Minimal Clinically Important Differences in Pharmacological Trials. Am J Respir Crit Care Med 2014 Feb 1; 189 (3): 250–255. Accessed February 10, 2021.

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Simon RH. Cystic fibrosis: Overview of the treatment of lung disease. In: UpToDate, Mallory GB, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on March 01, 2021.

Mogayzel PJ, Naureckas ET, Robinson KA, et al.: Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintenance of Lung Health. Am J Respir Crit Care Med 2013 Apr 1; 187 (7):680-689. Accessed on March 01, 2021.

Nevitt_SJ, Thornton_J, Murray_CS, Dwyer_T. Inhaled mannitol for cystic fibrosis. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD008649. DOI: 10.1002/14651858.CD008649.pub4. Accessed on March 01, 2021.