

## **mannitol (Bronchitol®)**

**Policy # 00734**

Original Effective Date: 07/12/2021

Current Effective Date: 07/01/2025

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider mannitol (Bronchitol®)† for the treatment of cystic fibrosis to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for mannitol (Bronchitol) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of Cystic Fibrosis; AND
- Patient is greater than or equal to 18 years of age; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) nebulized hypertonic saline unless there is patient history or clinical evidence that suggests the use of hypertonic saline therapy will be ineffective or cause an adverse response to the patient.

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*

### **When Services Are Considered Not Medically Necessary**

Based on review of available data, the Company considers the use of mannitol (Bronchitol) when the patient has not tried and failed nebulized hypertonic saline to be **not medically necessary.\*\***

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of mannitol (Bronchitol) when the patient selection criteria are not met (except those denoted above to be **not medically necessary\*\***) to be **investigational.\***

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## **Background/Overview**

Bronchitol contains the sugar alcohol, D-mannitol, and is indicated as add-on maintenance therapy in adults with Cystic Fibrosis (CF). It is a mucolytic with an unknown mechanism of action. Prior to initiation of Bronchitol, patients must pass the Bronchitol Tolerance Test (BTT) which must be performed under the supervision of a healthcare practitioner who is able to manage acute bronchospasm. For patients who have passed the BTT, the dose of Bronchitol is 400 mg twice a day by oral inhalation (the contents of 10 capsules administered individually). This dose should be preceded by administration of a short-acting bronchodilator 5-15 minutes before the dose. Additionally, the last dose of the day should be administered at least 2-3 hours prior to bedtime.

CF is a serious genetic disorder affecting the lungs and other organs. It is caused by mutations in a gene that encodes for a protein called CFTR that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes.

Symptomatic therapies for CF lung disease include a variety of airway clearance techniques as well as aerosolized agents for airway clearance. Although CFTR modulators (e.g., ivacaftor [Kalydeco<sup>®</sup>]<sup>‡</sup>, tezacaftor/ivacaftor [Symdeko<sup>®</sup>]<sup>‡</sup>, elexacaftor/tezacaftor/ivacaftor [Trikafta<sup>®</sup>]<sup>‡</sup>, lumacaftor/ivacaftor [Orkambi<sup>®</sup>]<sup>‡</sup>) correct the underlying CFTR defect, conventional therapies including aerosolized agents for airway clearance continue to have a pivotal role in maintaining well-being and improving survival. The two airway clearance agents used in the United States (prior to approval of Bronchitol) are dornase alfa [Pulmozyme<sup>®</sup>]<sup>‡</sup> and hypertonic saline. Pulmozyme is used by the majority of CF patients  $\geq 6$  years of age. It works by degrading DNA and decreasing mucus viscosity to improve pulmonary function via reduction in mucus viscoelasticity. Hypertonic saline is also used in many patients and is administered via nebulization. It is available as a generic product and also under various trade names (e.g., HyperSal<sup>®</sup>), but none are formally FDA-approved in CF. In a randomized controlled trial comparing either hypertonic or isotonic saline over 48 weeks, there was no significant improvement in the rate of FEV<sub>1</sub> decline. A Cochrane systematic review confirmed that hypertonic saline had a limited effect on lung function, but improved quality of life and reduced pulmonary exacerbations. Current US clinical guidelines from the CF Foundation (2013) strongly recommend chronic use of Pulmozyme in patients  $\geq 6$  years of age to improve lung function, quality of life, and reduce exacerbations. Chronic use of hypertonic saline is also recommended for patients  $\geq 6$  years of age to improve lung function and quality of life as well as to reduce exacerbations. Guidelines have not been updated to include Bronchitol.

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## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Bronchitol was approved in October 2020 as add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with Cystic Fibrosis. Bronchitol must only be used for adults who have passed the Bronchitol Tolerance Test.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Bronchitol for the treatment of cystic fibrosis was evaluated in 3 randomized, double-blind, controlled trials (Trials 1, 2, and 3). All three trials were 26 weeks in duration. Trial 1 evaluated 423 patients 18 years of age or older with baseline FEV<sub>1</sub> >40% to <90% of predicted. Trial 2 evaluated 295 patients 6 years of age or older with baseline FEV<sub>1</sub> ≥30% to <90% of predicted. Trial 3 evaluated 305 patients 6 years of age or older with baseline FEV<sub>1</sub> ≥40% to <90% predicted. All three trials excluded patients with an episode of hemoptysis (>60 mL) in the 3 months prior to enrollment. The use of inhaled hypertonic saline was not permitted in any of the three trials, but continued use of other standard of care cystic fibrosis therapies were allowed (e.g., bronchodilators, inhaled antibiotics, and dornase alfa). Note that while patients aged 6-17 years were included in Trials 2 and 3, the FDA has not approved Bronchitol in this age group.

In all three trials, patients were randomized to receive either Bronchitol 400 mg or control (50 mg inhaled mannitol) twice daily. Each dose of Bronchitol was preceded by use of an inhaled short-acting bronchodilator taken 5 to 15 minutes prior to initiation of Bronchitol dosing. The primary efficacy endpoint was improvement in lung function as determined by the mean change from baseline in pre-dose FEV<sub>1</sub> (mL) over 26 weeks of treatment. In Trial 1, the control group had an adjusted mean change of 12 mL and the Bronchitol group had an adjusted mean change of 63 mL (adjusted mean difference of 51 mL, p=0.028). In Trials 2 and 3, the treatment difference between Bronchitol and control was 68 mL (95% CI: 24 to 113 mL) and 52 mL (95% CI: -1 to 107 mL), respectively.

It should be noted that Bronchitol's efficacy was moderate in preserving lung function in adults. Additionally, two of these trials were conducted prior to availability of CFTR modulators and in the third trial no breakdown of CFTR modulator use was provided. Therefore, data do not reflect current clinical practice and use of Bronchitol with CFTR modulators is unknown.

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## **References**

1. Bronchitol [package insert]. Chiesi USA, Inc. Cary, NC. Updated November 2020.
2. Bronchitol Drug Evaluation. Express Scripts. Updated January 2021.
3. Southern KW, Clancy JP, Ranganathan S. Aerosolized agents for airway clearance in cystic fibrosis. *Pediatric Pulmonology*. 2019;54:858-864.
4. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Pulmonary clinical practice guidelines committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.

## **Policy History**

Original Effective Date: 07/12/2021

Current Effective Date: 07/01/2025

06/03/2021 Medical Policy Committee review

06/09/2021 Medical Policy Implementation Committee approval. New policy.

06/02/2022 Medical Policy Committee review

06/08/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/01/2023 Medical Policy Committee review

06/14/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/06/2024 Medical Policy Committee review

06/12/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/05/2025 Medical Policy Committee review

06/11/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2026

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.