Bronchitol (mannitol) inhalation powder

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Bronchitol (mannitol) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Bronchitol (mannitol) is a sugar alcohol indicated as add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis (CF).

Limitations of Use

Bronchitol is to be used only in adults who have passed the Bronchitol Tolerance Test.

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

- Bronchitol Tolerance Test (BTT) results
- Percent of predicted forced expiratory volume ($ppFEV_1$)

Initial Criteria for Approval

Bronchitol may be considered medically necessary for add-on maintenance therapy to improve pulmonary function in adult patients with cystic fibrosis when **ALL** of the following criteria are met:

1. The patient is 18 years of age or older and has a baseline percent of predicted forced expiratory volume (ppFEV1) of ≥ 30% to < 90%

2. The patient has taken and passed the Bronchitol Tolerance Test under the supervision of a healthcare practitioner who is able to manage acute bronchospasm and did not experience any of the following during the test [See Appendix]:
   a. Bronchospasm
   b. Decrease in FEV1
   c. Decrease in oxygen saturation
3. The patient has experienced an inadequate response to a maximally tolerated dose or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to hypertonic saline inhalation solution
4. The patient will perform airway clearance techniques (ACTs) while receiving therapy with Bronchitol
5. The patient will use a short-acting bronchodilator (e.g., albuterol, levalbuterol, etc.) by oral inhalation 5-15 minutes before each dose of Bronchitol
6. The patient will NOT use Bronchitol and hypertonic saline inhalation solution concomitantly

Initial approval will be granted for **6 months.**

Continuation of Therapy
Authorization of 12 months may be granted for continued treatment for members requesting reauthorization for add-on maintenance therapy to improve pulmonary function in cystic fibrosis who meet all initial criteria for approval AND are experiencing benefit from therapy as evidenced by disease improvement (e.g., improvement in FEV1 from baseline, etc.).

Bronchitol (mannitol) is considered **not medically necessary** for patients who do not meet the criteria set forth above.

Non-Formulary Exception Criteria
Non-Formulary Exception criteria applies to formularies which do not include the requested product(s) on the formulary drug list. Meeting the criteria above may satisfy some, or all, portions of the Non-Formulary Exception Criteria. A medication that is non-formulary may be covered when the Criteria for Approval AND the following criteria are met:

1. The requested drug must be used for an FDA-approved indication, or an indication supported in the compendia of current literature (examples: AHFS, Micromedex, current accepted guidelines). Diagnostic testing/lab results required when applicable.
2. The prescribed dose/quantity must fall within the FDA-approved labeling or dosing guidelines found in the compendia of current literature.
3. All covered formulary alternative drugs on any tier will be ineffective, have been ineffective, would not be as effective as the non-formulary drug, or would have adverse effects. Documentation is required and must include chart note(s) or other documentation indicating prior treatment failure, severity of the adverse event (if any), and dosage and duration of the prior treatment, or contraindication to formulary alternatives.

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits
- 4 inhalers/560 capsules per 28 days

Appendix
- Bronchitol Tolerance Test (BTT) Healthcare Practitioner (HCP) Instructions for Use (IFU) available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202049s000lbl.pdf or https://bronchitol.com/hcp/bronchitol-tolerance-test/

CLINICAL RATIONALE

Background

Bronchitol (mannitol) is an osmotic agent indicated as add-on maintenance therapy to improve pulmonary function in adult patients with CF. Other inhaled products approved for the treatment of CF include Pulmozyme (dornase alfa), Cayston (aztreonam), Bethkis (tobramycin), Kitabis Pak (tobramycin), Tobi (tobramycin), and Tobi Podhaler (tobramycin) (FDA, 2020a). The only other osmotic agent involved in the treatment of CF is inhaled hypertonic saline; however, it is not FDA approved for use in CF (FDA, 2020a; Bilton, 2011).

The CF Foundation has developed several different guidelines regarding different aspects of CF care, and the guidelines for chronic pulmonary health recommend the chronic use of Pulmozyme (dornase alfa) and inhaled hypertonic saline in patients 6 years of age and older regardless of disease severity (Mogayzel, 2013). The treatment guidelines also recommend azithromycin, Cayston (aztreonam), and inhaled tobramycin in patients 6 years of age and older with persistent *Pseudomonas aeruginosa* cultures. Of note, azithromycin should also be considered in patients 6 years of age and older without persistent *P. aeruginosa* cultures. In addition, the guidelines recommend against the prophylactic use of antistaphylococcal antibiotics as well as the routine use of inhaled or oral corticosteroids in patients without asthma or allergic bronchopulmonary aspergillosis.

Efficacy

The efficacy of Bronchitol (mannitol) for the treatment of CF was evaluated in three phase III, international, multicenter, 26-week, randomized, double-blind, controlled trials (N = 423 for Trial 1; N = 205 for Trial 2; N = 305 for Trial 3) (Aitken, 2011; Amelina, 2018; Bilton, 2011). Of note, Trial 1 was unpublished, and Trials 2 and 3 were published. Patients were randomized to receive either Bronchitol (mannitol) 400 mg inhaled twice daily or subtherapeutic mannitol 50 mg inhaled twice daily for the control group. Subtherapeutic mannitol was chosen for the control arm due to the need to maintain blinding, to provide an appropriate comparator, and to comply with scientific advice from regulatory agencies. Trial 1 evaluated patients 18 years of age and older with baseline percent of predicted forced expiratory volume (ppFEV1) of > 40% to <90%. Trial 2 evaluated patients 6 years of age and older with baseline ppFEV1 of ≥ 30% to < 90%. Trial 3 evaluated patients 6 years of age and older with baseline ppFEV1 of > 40% to < 90%. The primary outcome of all three trials was the improvement in lung function as determined by the absolute mean change from baseline in forced expiratory volume (FEV1). The mean age for Trial 1 was 27.7 years and the mean baseline ppFEV1 was 63.1%. The mean age for Trial 2 was 23 years, 96.3% of patients were White, 44.7% were female, 75.3% were receiving Pulmozyme (dornase alfa), the mean baseline ppFEV1 was 62.0%, and the average FEV1 was 2.02 L. The median age for Trial 3 was 18 years, 48.4% were female, 55.3% were receiving Pulmozyme (dornase alfa), the mean baseline ppFEV1 was 62.5%, and the average FEV1 was 2.02 L. The use of standard of care CF therapies was permitted, with the exception of hypertonic saline, in all three trials (Bronchitol prescribing information, 2020, 2020). All three trials excluded patients with an episode of hemoptysis > 60 mL in the 3 months prior to trial enrollment. The efficacy data from the three trials are summarized in Table 1. Bronchitol (mannitol) provided statistically and clinically significant improvement in FEV1 in Trials 1 and 2, but not Trial 3 (Aitken, 2011; Amelina, 2018; Bilton, 2011).
In terms of pulmonary exacerbations, both Trial 2 and Trial 3 provided data (Aitken, 2011; Bilton 2011). During Trial 2, there was a significant 35.4% reduction in the incidence of protocol-defined pulmonary exacerbations (PDPE) during the trial (p = 0.045), but there was no significant reduction in the exacerbation rate (Bilton, 2011). During Trial 3, there was no significant difference in PDPEs between the Bronchitol (mannitol) and control groups (Aitken, 2011). In a pooled analysis of the three trials, CF exacerbations occurred in 132 of 414 (32%) patients receiving Bronchitol (mannitol) and in 114 of 347 (33%) patients receiving control (i.e., inhaled mannitol 50 mg) (Bronchitol prescribing information, 2020). Study results are shown in Table 1.

Table 1: Efficacy of Bronchitol (mannitol) in the Treatment of Cystic Fibrosis

	Trial 1: Amelina, 2018		Trial 2: Bilton, 2011		Trial 3: Aitken, 2011	
Endpoints	**Bronchitol (n = 209)**	**Control (n = 214)**	**Bronchitol (n = 177)**	**Control (n = 118)**	**Bronchitol (n = 184)**	**Control (n = 121)**
Absolute difference in change from baseline in FEV_1 at 26 weeks	54 mL (95% CI 8 to 100) (p = 0.02)		92.9 mL (95% CI not available) (p < 0.001)		54.1 mL (95% CI -2 to 110.3) (p = NS)	

Safety

In clinical trials, the most commonly reported adverse events that occurred in ≥ 3% of study participants and more commonly than with placebo included cough, hemoptysis, oropharyngeal pain, bacteria found in sputum, pyrexia, vomiting, and arthralgia. Additionally, the proportions of patients reporting at least one adverse event were similar between the Bronchitol (mannitol) and control groups were similar for all three trials; of note, in Trial 2, cough, hemoptysis, and pharyngolaryngeal pain were more common in the Bronchitol (mannitol) group compared with the control group (Aitken, 2011; Amelina, 2018; Bilton, 2011).

Bronchitol (mannitol) has a warning for causing bronchospasm, which can be severe in susceptible individuals. Due to the risk of bronchospasm, patients must undergo the BTT to evaluate the eligibility for Bronchitol (mannitol) maintenance therapy. Bronchitol (mannitol) also has a warning for causing hemoptysis and should be discontinued if hemoptysis occurs.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- No applicable codes

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*Some content reprinted from CVS Health

POLICY HISTORY

Policy #: 05.04.30
Original Effective Date: March 17, 2021
Reviewed: April 2025
Revised: March 2021
Current Effective Date: June 5, 2021