mannitol (Bronchitol®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO219

Description

Mannitol (Bronchitol) is an orally administered sugar alcohol inhalation powder.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mannitol (Bronchitol)	40 mg capsules	Cystic Fibrosis	560 capsules/28 days

Initial Evaluation

I. **Mannitol (Bronchitol)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. A diagnosis of **Cystic Fibrosis** when the following are met:
      1. Provider attestation member has passed mannitol (Bronchitol) tolerance test; **AND**
      2. Treatment with hypertonic saline has been ineffective, contraindicated, or not tolerated

II. Mannitol (Bronchitol) is considered investigational when used for all other conditions, including but not limited to:
   A. Bronchiectasis
   B. Parkinson's Disease
   C. Chronic Obstructive Pulmonary Disease (COPD)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., improvement in FEV1, decrease in pulmonary exacerbations, decrease in hospitalization rate, improved quality of life].

Supporting Evidence

I. FDA approval for mannitol (Bronchitol) is based on three international, Phase 3, randomized, double blind, 26-week trials [CF301 (n=324), CF302 (n=318), CF303 (n=423)] which evaluated mannitol (Bronchitol) compared to subtherapeutic mannitol (control) in CF.
   - CF301 and CF302 included patients six years of age and older.
   - CF303 included adult patients only.

II. Trials CF301 and CF303 met their primary outcome of a change in FEV1 over 26 weeks. However, none of the trials met statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements.
   - CF301 Treatment difference: 92.9 mL (95% CI: Not Reported; P <0.001)
   - CF303 Treatment difference: 54 mL (95% CI: 8-100; P= 0.02)

III. Patients in the three clinical trials were able to continue use of dornase alfa (Pulmozyme); however, use of hypertonic saline was not permitted. To date, no studies have been conducted using mannitol (Bronchitol) concomitantly with hypertonic saline and there are no head-to-head trials comparing the two therapies. Safety and efficacy of concomitant use of mannitol (Bronchitol) and hypertonic saline has not been established.

IV. Although mannitol (Bronchitol) was evaluated in two trials that included pediatric patients (CF301 and CF302), safety and efficacy in this population remains uncertain. The manufacturer submitted data from pediatric trials CF301 and CF302 to the FDA in 2012 seeking approval in patients six years of age and older. The FDA issued a complete response letter due to inadequate efficacy as trial CF302 did not meet its primary endpoint, coupled with an increased risk of hemoptysis, especially in the pediatric population. The FDA then recommended a third study be completed to show efficacy evidence in adult patients and confirm an acceptable safety profile. Additionally, per the package insert, mannitol (Bronchitol) is not indicated for use in children and adolescents. The safety and effectiveness of mannitol (Bronchitol) has not been established in pediatric patients for cystic fibrosis. Patients aged six to 17 years were included in two 26-week, double-blind clinical trials (Trials CF301 and CF302). In these trials, 154 patients under 18 years of age received mannitol (Bronchitol) and 105 patients received control (50 mg inhaled mannitol). Hemoptysis was reported in 12 of 154 (7.8%) patients who received mannitol (Bronchitol) and in 2 of 105 (1.9%) patients who received control.

V. Guidelines recommend chronic use of hypertonic saline in CF patients regardless of lung disease severity (*Grade B, moderate recommendation*). Dornase alfa (Pulmozyme) is also recommended as maintenance therapy for all levels of lung disease severity (*Grade B, moderate*

recommendation), with a strong recommendation (*Grade A)* in those with moderate to severe disease. Guidelines have not been updated to include mannitol (Bronchitol) in the treatment CF.

VI. Given current guideline recommendations for use of hypertonic saline to improve lung function and quality of life and reduce exacerbations, coupled with lack of head-to-head trials comparing mannitol (Bronchitol) to hypertonic saline and lack of statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements with mannitol (Bronchitol) use in CF301, CF302, or CF303 studies, use of hypertonic saline prior to mannitol (Bronchitol) is required.

Investigational or Not Medically Necessary Uses

I. Mannitol (Bronchitol) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Bronchiectasis
     - i. A Phase 3 trial (NCT00669331) evaluating mannitol (Bronchitol) to control (50 mg mannitol) found use of mannitol (Bronchitol) in patients with clinically significant bronchiectasis did not significantly reduce exacerbation rates. Further evaluation is needed to confirm use of mannitol (Bronchitol) in this population.
   - B. Parkinson's Disease
     - i. As of December 2020, trials are currently recruiting in this setting.
   - C. COPD
     - i. Clinical trials evaluating mannitol (Bronchitol) in COPD were withdrawn due to recruitment failures.

References

1. Bronchitol [Prescribing Information]. Chiesi USA, Inc.: Cary, NC. October 2020.
2. Bilton D, Robinson P, Cooper P, et al. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. Eur Respir J. 2011;38(5):1071-1080.
3. Aitken ML, Bellon G, De Boeck K, et al. Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study. Am J Respir Crit Care Med. 2012;185(6):645-652.
4. Flume P, Amelina E, Krasko V, Carryer B, Charlton B, Leadbetter J, et al. The efficacy and safety of inhaled mannitol in adults with cystic fibrosis. Poster presented at: 31st North American Cystic Fibrosis Conference; 2017 Nov 2-4th; Indianapolis, IN
5. 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;187(7):680-689.
6. Nevitt SJ, Thornton J, Murray CS, Dwyer T. Inhaled mannitol for cystic fibrosis. Cochrane Cystic Fibrosis and Genetic Disorders Group, ed. Cochrane Database of Systematic Reviews. Published online May 1, 2020.
7. National Institute for Health and Care Excellence. Mannitol dry powder for inhalation for treating cystic fibrosis: Technology appraisal guidance. Published November 28, 2012. Available at: https://www.nice.org.uk/guidance/ta266/resources/mannitol-dry-powder-for-inhalation-for-treating-cystic-fibrosis-pdf-82600555351237
8. Bilton D, Tino G, Barker AF, et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax. 2014;69(12):1073-1079.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021