NEW DRUG APPROVAL

Brand Name	Bronchitol®
Generic Name	mannitol
Drug Manufacturer	Chiesi USA, Inc.

New Drug Approval

FDA Approval Date: October 30, 2020

Review Designation: Standard, Orphan

Type of Review: New Drug Application (NDA): 202049

Dispensing Restrictions: None

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cystic fibrosis (CF) is an inherited autosomal recessive genetic disease caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein functions as a chloride membrane channel in cells of the exocrine system that produce mucus, sweat, saliva, tears, and digestive enzymes. The protein controls the movement of chloride ions into and out of cells, which also determines the movement of water across cells.

Mutations in the CFTR protein gene lead to the creation of a dysfunctional protein, causing cells to produce mucus that is abnormally thick and sticky. CF is a progressive, multi-organ disease with the greatest impact on the lungs. Abnormal mucus in the lungs decreases mucociliary clearance, which can lead to airway obstruction, inflammation, and infection. Over time, significant damage happens to lung parenchyma. In CF, advanced cystic fibrosis lung disease is the most frequent cause of death. FEV1 is the strongest clinical predictor of survival among patients with CF, and it is commonly used to measure disease severity, progression, and therapeutic response.

Approximately 30,000 people have cystic fibrosis (CF) in the United States, and about 1000 new cases are diagnosed each year. The disorder is most prevalent among Caucasians, occurring in approximately one of every 3200 live Caucasian births. CF is also present in other races, but with a much lower incidence.

- Adults 18 years and older represent 52.7% of the CF population.
- Approximately 70% of CF patients are 12 years and older.
- Homozygous F508del mutation occurs in 45.8% of all people with CF.

Efficacy

The efficacy of Bronchitol® for the treatment of cystic fibrosis (CF) was evaluated in 3 randomized, double-blind, controlled trials (Trials 1, 2, and 3).

All three trials were 26-week, randomized, double-blind, controlled studies in patients with CF.
Trial 1 (NCT02134353) evaluated patients 18 years of age or older with baseline FEV1 >40% to <90% of predicted.
Trial 2 (NCT00446680) evaluated patients 6 years of age or older with baseline FEV1>30% to <90% of predicted.
Trial 3 (NCT00630812) evaluated pateints 6 years of age or older with baseline FEV1>40% to <90% of predicted. All three trials excluded CF 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 their other standard of care CF therapies were allowed (e.g., bronchodilators, inhaled antibiotics, and dornase alfa). While CF patients aged 6 to 17 years were included in Trials 2 and 3, Bronchitol® is not indicated for use in this age group.

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 (albuterol or equivalent) taken 5 to 15 minutes prior to initiation of Bronchitol® dosing. The primary efficacy endpoint in all three studies was improvement in lung function as determined by the mean change from baseline in pre-dose FEV1 (mL) over 26 weeks of treatment and was analyzed using the pattern mixture model with multiple imputation.

Trial 1 evaluated 423 adult patients with a mean age of 28 years and a mean FEV1 63.9% predicted (range: 40.3% = minimum, 89.6% = maximum). Treatment with Bronchitol® resulted in a statistically significant improvement in FEV1. In Trial 1, the treatment difference between Bronchitol® and control for the adjusted mean change in FEV1 from baseline over 26 weeks was 51 mL (95% CI 6 to 97 mL) shown in Table 2.

Table 2: Change in FEV_1 (mL) from Baseline Over 26 weeks by Treatment Group (Trial 1, intention to treat population)

	Control (N=214)	BRONCHITOL (N=209)
Adjusted mean change from baseline	12 mL	63 mL
Adjusted mean difference (95% CI), p-value	51 mL (6 to 97 mL), p=0.028	

Trials 2 and 3 evaluated 295 and 305 patients, respectively. For the adjusted mean difference in the change from baseline in FEV1 over 26 weeks in the intention-to-treat population 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: -3 to 107 mL), respectively. Post-hoc descriptive analyses of the adult subgroups from Trials 2 and 3 were performed. The adult subgroup analyses in Trial 2 and 3 evaluated 209 and 157 adult patients, respectively. In Trial 2, there was an adjusted mean difference in the change from baseline in FEV1 over 26 weeks in the intention-to-treat population of adults of 78 mL (95% CI: 21 to 135 mL). In Trial 3, there was an adjusted mean difference in the change from baseline in FEV1 over 26 weeks in the intention-to-treat population of adults of 78 mL (95% CI: 2 to 153 mL).

The new drug application (NDA) for Bronchitol was initially submitted to the FDA in 2012 for patients 6 years of age and older with CF. Bronchitol received a complete response letter (CRL) due to inadequate efficacy results from the two Phase 3 clinical trials (studies 301 and 302) and due to an increased risk of hemoptysis, especially in the pediatric population. The FDA recommended a third study be completed to show evidence of efficacy in adult patients and to confirm an acceptable safety profile. Throughout the clinical trial program, the “placebo” therapy was a low dose (50 mg) of mannitol inhalation powder to address blinding concerns related to the sweet taste of mannitol. Chiesi resubmitted the NDA in 2018 for adults 18 years of age and older. The FDA and an advisory panel focused on the results from a third study, Study 303, which looked at improvements in FEV1 over 26 weeks compared to baseline (same primary endpoint as the first two studies). Results showed a statistically significant improvement in lung function in treated patients when compared to placebo, but the benefit was modest, with an adjusted mean difference of 0.054 L (95% CI: 0.008; 0.100), P = 0.020. The advisory panel expressed uncertainty about the clinical benefit, given the modest improvement in FEV1. Of note, studies 302 and 303 did not show a benefit with inhaled mannitol with respect to reduction in pulmonary exacerbations, with some results even showing a numerical increase in the treatment arm versus the control arm. The use of inhaled hypertonic saline was not permitted in any of the three trials, but continued use of patients’ other standard of care CF therapies (e.g. bronchodilators, inhaled antibiotics, and dornase alfa) were allowed.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥3%) include cough, hemoptysis, oropharyngeal pain, vomiting, bacteria sputum identified, pyrexia, and arthralgia.

WARNINGS & PRECAUTIONS

- Bronchitol® can cause bronchospasm, which can be severe in susceptible patients. Because of the risk of bronchospasm, prior to prescribing Bronchitol®, perform the Bronchitol® tolerance test (BTT). The BTT must be administered under the supervision of a healthcare practitioner who can treat severe bronchospasm. Do not prescribe Bronchitol® if the patient fails the BTT. Patients who pass the BTT may experience bronchospasm with maintenance use of Bronchitol®. Advise patients to premedicate with an inhaled shortacting bronchodilator prior to each administration of Bronchitol®. If bronchospasm occurs, immediately discontinue Bronchitol®. Treat bronchospasm with an inhaled short-acting bronchodilator.
- Hemoptysis can occur with Bronchitol® use. Monitor patients with history of episodes of hemoptysis. If hemoptysis occurs, discontinue use of Bronchitol®.

CONTRAINDICATIONS

- Hypersensitivity to mannitol or to any of the capsule components.
- Failure to pass the Bronchitol® Tolerance Test.

Clinical Pharmacology

MECHANISMS OF ACTION

The precise mechanism of action of Bronchitol® in improving pulmonary function in cystic fibrosis patients is unknown.

Dose & Administration

ADULTS

The recommended dosage of Bronchitol® is 400 mg twice a day by oral inhalation (the contents of 10 capsules administered individually) via the inhaler (For patients who have passed the BTT).

PEDIATRICS

Bronchitol® is not indicated for use in children and adolescents. The safety and effectiveness of Bronchitol® have not been established in pediatric patients for cystic fibrosis.

GERIATRICS

Clinical trials of Bronchitol® did not include sufficient numbers of patients with cystic fibrosis who were 65 years of age and older to allow evaluation of safety and efficacy in this population.

RENAL IMPAIRMENT

Clinical trials of Bronchitol® did not include patients with renal impairment. No specific dose recommendations for renal patient population is available. However, an increase in systemic exposure of mannitol can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

HEPATIC IMPAIRMENT

Clinical trials of Bronchitol® did not include patient with hepatic impairment. No specific dose recommendations for hepatic patient population is available.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Inhalation powder: 40 mg mannitol per capsule