PDL DRUG REVIEW

Proprietary Name: Bronchitol®
Common Name: mannitol
PDL Category: Cystic Fibrosis Agents

Summary

Pharmacology/Usage: D-Mannitol (referred to throughout as mannitol), the active ingredient of Bronchitol®, is a hexahydric sugar alcohol. The exact mechanism of action for its approved indication is not known.

Indication: As add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with cystic fibrosis (CF). Use Bronchitol® only for adults who have passed the Bronchitol® Tolerance Test (BTT). (see Recommended Dosage section for further information)

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate and well-controlled studies of use in pregnant women. The available data on use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. There are risks to the mother associated with CF in pregnancy. Bronchitol® should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Inhalation Powder: 40mg mannitol per capsule. Available as a blister pack co-packaged with an inhaler.

The Bronchitol® inhaler should be discarded and replaced after 7 days of use. If the inhaler does need to be washed, the patient should allow the inhaler to thoroughly air dry before next use. Instruct on correct inhaler use, including loading of capsules and proper inhalation technique.

Recommended Dosage: For patients who have passed the BTT, the recommended dosage is 400mg BID by oral inhalation (the contents of 10 capsules administered individually) via the inhaler. A short-acting bronchodilator should be administered by oral inhalation, 5-15 minutes before every dose of Bronchitol®. Bronchitol® should be taken once in the morning and once in the evening, with the later dose taken at least 2-3 hours before bedtime.

Prior to prescribing Bronchitol® for CF treatment, the Bronchitol® Tolerance Test (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® maintenance therapy.

- Perform BTT to identify patients who experience bronchospasm, a decrease in FEV1, or a decrease in oxygen saturation with administration of Bronchitol®. If a patient experiences any of these events during the BTT, the patient has failed the BTT. Do not prescribe Bronchitol®. If a patient does not experience any of these events during BTT, the patient has passed the BTT and is a candidate for Bronchitol® therapy.
- Ensure that rescue medication and resuscitation equipment are available for immediate use during the BTT.
- Do not perform the BTT if the patient is considered clinically unstable.

- See the BTT Healthcare Practitioner (HCP) instructions for use for complete instructions and to avoid medication errors associated with BTT dosing and procedures.

Do not use Bronchitol® add-on maintenance therapy in patients who fail the BTT.

Clinical trials of Bronchitol® did not include patients with renal or hepatic impairment. No specific dose recommendations for these patient populations are 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.

Drug Interactions: No formal drug interaction studies have been conducted with mannitol.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Bronchitol®) minus reported % incidence for control. Please note that an incidence of 0% means the incidence was the same as or less than the control.* The most frequently reported adverse events included cough (4.3%), hemoptysis (0.9%), oropharyngeal pain (2.7%), vomiting (1.7%), bacterial sputum identified (2.2%), pyrexia (2.3%), and arthralgia (0.5%).

Bronchitol® can cause bronchospasm, which can be severe in susceptible individuals. Because of the risk of bronchospasm, prior to prescribing Bronchitol®, perform the BTT, to identify patients who are appropriate for maintenance treatment with Bronchitol®. The BTT must be administered under the supervision of a healthcare provider who can treat severe bronchospasm. Do not prescribe Bronchitol® if the patient fails the BTT.

Bronchospasm may occur during inhalation of Bronchitol®, even in patients who have passed the BTT. An inhaled short-acting bronchodilator must be administered 5-15 minutes before administration of each dose during maintenance therapy. In clinical studies, bronchospasm or bronchial hyperreactivity was reported in 1% of those receiving Bronchitol® as maintenance therapy and in 0.6% receiving control (50mg inhaled mannitol), even though these patients had passed the BTT. If bronchospasm occurs following dosing of Bronchitol®, it should be discontinued immediately and treated with an inhaled short-acting bronchodilator or as medically appropriate.

Hemoptysis may occur with Bronchitol® use. Hemoptysis was reported in 10.4% of adult patients receiving Bronchitol® and in 9.5% of adults receiving control (50mg inhaled mannitol) during clinical studies. In patients aged 6 years to 17 years, hemoptysis was reported in 7.8% of patients who received Bronchitol® and in 1.9% of patients who received control. Bronchitol® has not been studied in patients with a history of episodes of significant hemoptysis (volume greater than 60ml) in the previous 3 months. Bronchitol® should be discontinued in the event of hemoptysis. Note that Bronchitol® is not indicated for use in children and adolescents.

Contraindications: In the following conditions:

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

Manufacturer: Chiesi USA, Inc

Analysis: The safety and efficacy of Bronchitol® for the treatment of CF were assessed in 3 randomized, double-blind, controlled studies that were 26 weeks in duration. Study 1 included adults ≥18 years of age with baseline FEV1 >40 to <90% of predicted. The mean age of included adults in study 1 was 28 years and they had a mean FEV1 63.9% predicted. Study 2 included patients ≥6 with baseline FEV1 ≥30% to <90% of predicted, and study 3 included patients ≥6 years with baseline FEV1 ≥40% to <90% predicted. All 3 studies excluded CF patients with an episode of hemoptysis (>60ml) in the 3 months prior to enrollment. The use of inhaled hypertonic saline was not permitted in any of the studies but continued use of the 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 studies 2 and 3, Bronchitol® is not indicated for use in this age group.

Patients were randomized to receive either Bronchitol® 400mg or control (50mg inhaled mannitol) BID, and each Bronchitol® dose 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 3 studies was improvement in lung function as determined by the mean change from baseline in pre-dose FEV1 (ml) over 26 weeks and was analyzed using the pattern mixture model with multiple imputation.

Results suggested that treatment with Bronchitol® resulted in a statistically significant improvement in FEV1. In study 1, the treatment difference between Bronchitol® and control for the adjusted mean change in FEV1 from baseline over 26 weeks was 51ml. Results can be seen in the table below, which was adapted from the prescribing information.

	Control (N=214)	Bronchitol® (N=209)
Adjusted mean change from baseline	12 ml	63ml
Adjusted mean difference, p-value	51ml; p=0.028	

Trials 2 and 3 assessed 295 and 305 patients, respectively. For the adjusted mean difference in the change from baseline in FEV1 over 26 weeks in studies 2 and 3, the treatment difference between Bronchitol® and control was 68ml and 52ml, respectively.

Post-hoc descriptive analyses of the adult subgroups from studies 2 and 3 were performed. The adult subgroup analyses in trials 2 and 3 assessed 209 and 157 adults, respectively. In trial 2, there was an adjusted mean difference in the change from baseline in FEV1 over 26 weeks in adults of 78ml. In trial 3, there was an adjusted mean difference in the change from baseline in FEV1 over 26 weeks in adults of 78ml.

Place in Therapy: Bronchitol® is indicated as add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with CF. Use Bronchitol® only for adults who have passed the Bronchitol® Tolerance Test. A short-acting bronchodilator should be administered by oral inhalation 5-15 minutes before every dose of Bronchitol®. The safety and efficacy of use were assessed in 3 double-blind studies as compared with a control of 50mg inhaled mannitol. Study one included only adults and treatment with Bronchitol® resulted in a statistically significant improvement in FEV1; the treatment difference between Bronchitol® and control for the adjusted mean change in FEV1 from baseline over 26 weeks was 51ml.

It is recommended that Bronchitol® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Bronchitol [package insert]. Cary, NC: Chiesi USA, Inc; 2020.