

BRONCHITOL- mannitol capsule

Chiesi USA, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRONCHITOL safely and effectively. See full prescribing information for BRONCHITOL.

BRONCHITOL® (mannitol) inhalation powder, for oral inhalation use

Initial U.S. Approval: 1964

INDICATIONS AND USAGE

BRONCHITOL 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. Use BRONCHITOL only in adults who have passed the BRONCHITOL Tolerance Test. (1)

DOSAGE AND ADMINISTRATION

- For Oral Inhalation Only. (2.1)
- The BRONCHITOL Tolerance Test is administered to identify patients who are appropriate for inhaled mannitol use. (2.1)
- Treatment of cystic fibrosis: 400 mg of BRONCHITOL (10 capsules) twice a day by oral inhalation, in the morning and evening, with the later dose taken 2-3 hours before bedtime. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation powder: 40 mg mannitol per capsule (3)

CONTRAINDICATIONS

- Hypersensitivity to mannitol or to any of the capsule components. (4)
- Failure to pass the BRONCHITOL Tolerance Test. (4)

WARNINGS AND 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 short-acting bronchodilator prior to each administration of BRONCHITOL. If bronchospasm occurs, immediately discontinue BRONCHITOL. Treat bronchospasm with an inhaled short-acting bronchodilator. (2.1, 5.1)
- Hemoptysis can occur with BRONCHITOL use. Monitor patients with history of episodes of hemoptysis. If hemoptysis occurs, discontinue use of BRONCHITOL (5.2)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 3\%$) include cough, hemoptysis, oropharyngeal pain, vomiting, bacteria sputum identified, pyrexia, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRONCHITOL is indicated as add-on maintenance therapy to improve pulmonary function in adult patients 18 years and older with Cystic Fibrosis. Use BRONCHITOL only for adults who have passed the BRONCHITOL Tolerance Test [see *Dosage and Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Required Testing and Evaluation Prior to Prescribing BRONCHITOL (BRONCHITOL Tolerance Test)

Prior to prescribing BRONCHITOL for treatment of cystic fibrosis, 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 (IFU) 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 [see *Contraindications (4)*].

2.2 Recommended Dosage for Treatment of Cystic Fibrosis

For patients who have passed the BTT, the recommended dosage of BRONCHITOL is 400 mg twice a day by oral inhalation (the contents of 10 capsules administered individually) via the inhaler [see *Dosage and Administration (2.1)*].

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.

2.3 Use and Maintenance of Inhaler

Instruct patients on safe hygiene practices (clean and dry hands thoroughly) and correct inhaler use, including loading of capsules and proper inhalation technique per the Patient Instructions for Use.

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.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: 40 mg mannitol per capsule; clear, colorless hard gelatin capsule imprinted with "PXS 40 mg"

4 CONTRAINDICATIONS

BRONCHITOL is contraindicated in the following conditions:

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

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

BRONCHITOL Tolerance Test

BRONCHITOL can cause bronchospasm, which can be severe in susceptible individuals. Because of the risk of bronchospasm, prior to prescribing BRONCHITOL, perform the BRONCHITOL Tolerance Test (BTT), to identify patients who are appropriate for maintenance treatment with BRONCHITOL. The BTT must be administered under the supervision of a healthcare practitioner who can treat severe bronchospasm. In clinical trials, 896 adult patients with cystic fibrosis underwent the BTT and 72 patients (8%) failed or did not complete the BTT. Do not prescribe BRONCHITOL if the patient fails the BTT.

Maintenance Therapy

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 4 of 414 adult patients (1.0%) receiving BRONCHITOL as maintenance therapy and in 2 of 347 adult patients (0.6%) receiving control (50 mg inhaled mannitol), even though these patients had passed the BTT. If bronchospasm occurs following dosing of BRONCHITOL, it should immediately be discontinued and treated with an inhaled short-acting bronchodilator or as medically appropriate.

5.2 Hemoptysis

Hemoptysis may occur with BRONCHITOL use. Hemoptysis was reported in 43 (10.4%) adult patients receiving BRONCHITOL and in 33 (9.5%) adult patients receiving control (50 mg inhaled mannitol) during clinical studies. In patients aged 6 years to 17 years, hemoptysis was reported in 12 of 154 (7.8%) patients who received BRONCHITOL and in 2 of 105 (1.9%) patients who received control. BRONCHITOL has not been studied in patients with a history of episodes of significant hemoptysis (volume greater than 60 mL) in the previous 3 months. BRONCHITOL should be discontinued in the event of hemoptysis. BRONCHITOL is not indicated for use in children and adolescents.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Bronchospasm [*see Warnings and Precautions (5.1)*]
- Hemoptysis [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety profile for BRONCHITOL is based on data from 1,020 CF patients from three 26-week, randomized, double-blind, controlled trials (Trials 1, 2, and 3). While CF patients aged 6 to 17 years were included in two of the three trials, BRONCHITOL is not indicated for use in this age group [*see Indications (1), Use in Specific Populations (8)*].

The safety data described below are based on 761 adult patients who received at least one dose of study drug in the three trials.

Of the 761 adult patients, 45% of patients were female and 98% were Caucasian; 414 received BRONCHITOL and 347 received control (50 mg inhaled mannitol) for up to 26 weeks. Adult patients treated with BRONCHITOL were ages 18 to 59 years with a mean baseline FEV₁ of 62.0% of predicted.

In these three trials, the proportion of adult patients who prematurely discontinued study drug due to adverse reactions was 12.3% for patients treated with BRONCHITOL and 8.6% for patients treated with control. Serious adverse reactions occurred in 18.8% of patients treated with BRONCHITOL and 18.4% of patients treated with control. Serious adverse reactions occurring with greater than 1% incidence and more frequently in BRONCHITOL-treated adult patients compared to control-treated patients were CF exacerbations (13.3% vs. 11.2%), hemoptysis (1.4% vs. 1.2%) and lower respiratory tract infection (1.2% vs 0.9%).

The incidence of Adverse Reactions in adults during the 26 week treatment period with BRONCHITOL across the three trials is shown in Table 1.

Table 1. Adverse Reactions Occurring With \geq 3% Incidence and More Common Than Control in Adult CF Patients (Trials 1, 2, and 3)

Primary System Organ Class Preferred Term	BRONCHITOL N = 414 %	CONTROL N = 347 %
Respiratory, thoracic, and mediastinal disorders		
Cough	15.0	10.7
Hemoptysis	10.4	9.5
Oropharyngeal pain	7.0	4.3
Gastrointestinal disorders		
Vomiting	3.1	1.4
Investigations		
Bacteria sputum identified	6.8	4.6
General disorders and administrative site conditions		
Pyrexia	4.6	2.3
Musculoskeletal and connective tissue disorders		
Arthralgia	3.1	2.6

In Trials 1, 2, and 3, exacerbations of cystic fibrosis (reported as condition aggravated) occurred in 132 of 414 (32%) adult patients receiving BRONCHITOL and in 114 of 347 (33%) adult patients receiving control (50 mg inhaled mannitol). Exacerbations of cystic fibrosis reported as serious adverse reactions occurred in 55 of 414 adult patients (13%) receiving BRONCHITOL and in 39 of 347 adult patients (11%) receiving control. Within the U.S. adult subgroup (comprising 27% of adults enrolled), exacerbations of cystic fibrosis reported as serious adverse reactions occurred in 23 of 110 (21%) patients receiving BRONCHITOL and in 10 of 93 (11%) patients receiving control. Among the non-U.S. adult subgroup (comprising 73% of adults enrolled), exacerbations of cystic fibrosis reported as serious adverse reactions occurred in 11% of patients in each

treatment arm.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with mannitol, the active ingredient in BRONCHITOL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BRONCHITOL in pregnant women. The available data on BRONCHITOL use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. Based on animal reproduction studies, no evidence of structural alterations was observed when mannitol was administered to pregnant rats and mice during organogenesis at doses up to approximately 20 and 10 times, respectively, the maximum recommended daily inhalation dose (MRDID) in humans [see *Data*]. There are risks to the mother associated with cystic fibrosis in pregnancy [see *Clinical Considerations*]. BRONCHITOL should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Cystic fibrosis may increase the risk for preterm delivery.

Data

Animal Data

In animal reproduction studies, oral administration of mannitol to pregnant rats and mice during the period of organogenesis did not cause fetal structural alterations. The mannitol dose in rats and mice was approximately 20 and 10 times the maximum recommended human daily inhalation dose (MRDID) in humans, respectively, (on a mg/m² basis at maternal doses of 1600 mg/kg/day in both species).

8.2 Lactation

Risk Summary

It is not known whether BRONCHITOL is excreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRONCHITOL and any potential adverse effects on the breastfed child from BRONCHITOL or from the underlying maternal condition.

8.4 Pediatric Use

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. Patients aged 6 years to 17 years were included in two 26-week, double-blind clinical trials (Trials 2 and 3). In these trials, 154 patients under 18 years of age received BRONCHITOL and 105 patients received control (50 mg inhaled mannitol). Hemoptysis was reported in 12 of 154 (7.8%) patients who received BRONCHITOL and in 2 of 105 (1.9%) patients who received control.

8.5 Geriatric Use

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.

8.6 Hepatic and Renal Impairment

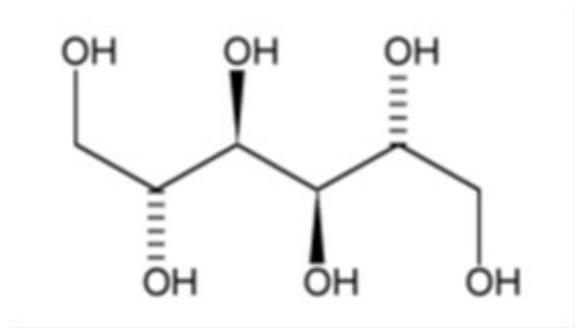
Clinical trials of BRONCHITOL did not include patients with hepatic or renal impairment. No specific dose recommendations for these patient populations are available. However, an increase in systemic exposure of mannitol can be expected in patients with renal impairment based on the kidney being its primary route of elimination.

10 OVERDOSAGE

Susceptible persons may experience bronchoconstriction from an overdose. If excessive coughing and bronchoconstriction occurs, immediately administer an inhaled short-acting bronchodilator and other medical treatments as necessary.

11 DESCRIPTION

BRONCHITOL (mannitol) inhalation powder contains D-Mannitol (referred to throughout as mannitol) as the active ingredient. Mannitol is a hexahydric sugar alcohol, with the following chemical name hexane-1,2,3,4,5,6-hexol and chemical structure:



Mannitol is a white or almost white crystalline powder or free-flowing granules with an empirical formula of $C_6H_{14}O_6$ and molecular weight of 182.2. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

BRONCHITOL contains mannitol powder spray dried into particles of respirable size filled into clear, colorless hard gelatin capsules. There are no inactive ingredients in BRONCHITOL.

The accompanying white plastic inhaler is comprised of a mouthpiece, blue piercing buttons, capsule chamber, and a removable cap. A blister pack consists of 10 capsules, each containing 40 mg mannitol. After a capsule is placed in the capsule chamber and pierced by firmly pressing and releasing the buttons on the side of the device, the powder within the capsule becomes exposed and ready for dispersion into the airstream generated by the patient upon inhalation through the mouthpiece. Under standardized *in vitro* test conditions, the inhaler delivers 32.2 mg of mannitol per inhalation when tested at a flow rate of 60 L/min for 2 seconds. The actual amount of drug delivered to the lungs will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

The pharmacodynamics of mannitol are unknown.

12.3 Pharmacokinetics

Absorption

Following oral inhalation of 635 mg, the mean mannitol peak plasma concentration (C_{max}) was 13.71 mcg/mL while the mean extent of systemic exposure (AUC) was 73.15 mcg•hr/mL. The mean time to peak plasma concentration (T_{max}) after oral inhalation was 1.5 hour.

Distribution

Based on intravenous administration, the volume of distribution of mannitol was 34.3 L.

Elimination

Metabolism

Mannitol is metabolized in a CYP-independent manner through the glycolytic pathway via dehydrogenation to fructose. The extent of metabolism of mannitol appears to be small. This is evident from a urinary excretion of about 87% of unchanged drug after an intravenous dose to healthy patients.

Excretion

Following oral inhalation, the elimination half-life of mannitol was 4.7 hours. The mean terminal elimination half-life for mannitol in plasma remained unchanged regardless of the route of administration (oral, inhalation, and intravenous). The urinary excretion rate versus time profile for mannitol was consistent for all routes of administration. The total clearance after intravenous administration was 5.1 L/hr while the renal clearance was 4.4 L/hr. Therefore, the clearance of mannitol was predominately via the kidney. Following

inhalation of 635 mg of mannitol in 18 healthy patients, about 55% of the total dose was excreted in the urine as unchanged mannitol. Following oral or intravenous administration of a 500 mg dose, the corresponding values were 54% and 87% of the dose, respectively.

Specific Populations

Patients with Hepatic and Renal Impairment: Formal pharmacokinetic studies using BRONCHITOL have not been conducted in patients with hepatic or renal impairment. Since the drug is eliminated primarily via the kidney, an increase in systemic exposure can be expected in renally impaired patients.

Drug Interaction Studies

No formal drug interaction studies have been conducted with BRONCHITOL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies in rats and mice mannitol did not show evidence of carcinogenicity at oral dietary concentrations up to 5% (or 7,500 mg/kg on a mg/kg basis). These doses were approximately 55 and 30 times the MRHDID, respectively, on a mg/m² basis.

Mutagenesis

Mannitol tested negative in the following assays: bacterial gene mutation assay, *in vitro* mouse lymphoma assay, *in vitro* chromosomal aberration assay in WI-38 human cells, *in vivo* chromosomal aberration assay in rat bone marrow, *in vivo* dominant lethal assay in rats, and *in vivo* mouse micronucleus assay.

Impairment of Fertility

The effect of inhaled mannitol on fertility has not been investigated.

14 CLINICAL STUDIES

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 patients 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 [see *Indications (1), Warnings and Precautions (5)*,

Adverse Reactions (6), Use in Specific Populations (8)].

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 FEV₁ (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).

16 HOW SUPPLIED/STORAGE AND HANDLING

BRONCHITOL (mannitol) inhalation powder:

- 40 mg of mannitol per capsule
- capsules are clear, colorless and imprinted in black with “PXS” on cap and “40 mg” on body
- supplied in cartons containing 10, 140 or 560 capsules in blister packs co-packaged with 1, 1, and 4 inhalers respectively in a carton

BRONCHITOL is provided in 3 commercial

presentations:

Pack Quantities	Inhalers	Capsules	NDC Number
4-week Treatment Pack (4 x 7-day treatment packs)	4	560	10122-212-56
7-day Treatment Pack	1	140	10122-212-14
Bronchitol Tolerance Test	1	10	10122-212-04

BRONCHITOL should be stored between 68°F-77°F (20°C-25°C) with excursions permitted between 59°F-86°F (15°C-30°C). [See USP Controlled Room Temperature]. Do not refrigerate. Do not freeze.

The Training Kit (NDC 10122-216-01), containing empty gelatin capsules, should be stored between 68°F-77°F (20°C-25°C) with excursions permitted from 59°F-86°F (15°C-30°C).

BRONCHITOL should only be used with the provided inhaler, which is a white plastic inhaler comprised of a mouthpiece, blue piercing buttons, capsule chamber, and a removable cap. All remaining unused (opened and unopened) blister packs and the inhalers should be properly discarded. Be sure to read the accompanying BRONCHITOL instructions completely before administration. If you have any questions, contact the supplier at 1-888-661-9260.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Patient Instructions for Use).

BRONCHITOL Tolerance Test

Inform patients that a BRONCHITOL Tolerance Test is required prior to beginning treatment with BRONCHITOL. The BRONCHITOL Tolerance Test must be performed by a healthcare practitioner equipped to monitor oxygen saturation (SpO₂), perform spirometry (FEV₁), and manage acute bronchospasm.

Inhaled Short-Acting Bronchodilator Use

Instruct patients that an inhaled short-acting bronchodilator such as albuterol must always be administered 5 to 15 minutes prior to every dose of BRONCHITOL.

Bronchospasm

Prior to administration, inform patients that bronchospasm can occur with inhalation of

BRONCHITOL. If patient experiences bronchospasm, instruct the patient to discontinue BRONCHITOL and contact their healthcare practitioner right away.

Hemoptysis

Inform patients that hemoptysis can occur with inhalation of BRONCHITOL. If a patient experiences hemoptysis, instruct patients to discontinue BRONCHITOL and contact their healthcare practitioner right away.

Administration

Instruct patients on the proper administration of BRONCHITOL with the inhaler. The recommended dosage is 10 capsules (400 mg) twice a day. This requires inhaling the contents of 10 capsules administered individually once in the morning and once at least 2-3 hours before bed.

Manufactured by:

Pharmaxis Ltd

20 Rodborough Rd

Frenchs Forest NSW 2086

AUSTRALIA

Manufactured for:

Chiesi USA, Inc.

Cary, NC 27518

USA

BRONCHITOL® is a registered trademark of Pharmaxis Ltd

CTBR-001-1120-01-SPL-1

HEALTHCARE PRACTITIONER INSTRUCTIONS FOR USE

HEALTHCARE PRACTITIONER INSTRUCTIONS FOR USE

Bronchitol[®]
(mannitol) inhalation powder

40 mg per capsule
FOR ORAL INHALATION ONLY

BRONCHITOL Tolerance Test (BTT)

The BTT identifies patients who are hyperresponsive to BRONCHITOL (inhaled mannitol) through a series of monitored inhalations of increasing doses. The BTT must be performed by a healthcare provider who is able to manage acute bronchospasm.

STOP the BTT if the patient:

- Has SpO₂ or FEV₁ measurements that fall below the STOP values calculated in STEP A
- Shows any signs of significant bronchoconstriction requiring treatment with a bronchodilator, such as wheezing or shortness of breath
- Experiences a distressing cough, vomiting, or any other signs that they are not tolerating BRONCHITOL
- Has not inhaled the contents of a total of 10 capsules during STEPS C through F; schedule a repeat BTT

Start here and record values below.

STEP	Pre-assessment calculations	STOP values
A	Measure baseline SpO ₂ and FEV ₁ values. Calculate STOP values.	Today's baseline SpO ₂ : _____ % x 0.9 = _____ % Today's baseline FEV ₁ : _____ L x 0.8 = _____ L
B	Instruct patient to use an inhaled short-acting beta-agonist.	While waiting: <input type="checkbox"/> Instruct patient to wash and dry hands. <input type="checkbox"/> Review all inhaler use steps.
C	Follow steps 1-8 on the right. Instruct patient to inhale contents of 1 capsule. Open inhaler, CONFIRM powder has been inhaled.	Record new SpO ₂ . SpO ₂ : _____ % Is new SpO ₂ more than 80-STOP ? <input type="checkbox"/> NO <input type="checkbox"/> YES
D	Follow steps 3-8 on the right. Instruct patient to inhale contents of 2 capsules, one capsule at a time. Open inhaler, CONFIRM powder has been inhaled.	Record new SpO ₂ and new FEV ₁ . SpO ₂ : _____ % FEV ₁ : _____ L Are both of the following true? <input type="checkbox"/> New SpO ₂ is more than 80-STOP ? <input type="checkbox"/> New FEV ₁ is more than 80-STOP ? <input type="checkbox"/> NO to either <input type="checkbox"/> YES to both
E	Follow steps 3-8 on the right. Instruct patient to inhale contents of 3 capsules, one capsule at a time. Open inhaler, CONFIRM powder has been inhaled.	Record new SpO ₂ and new FEV ₁ . SpO ₂ : _____ % FEV ₁ : _____ L Are both of the following true? <input type="checkbox"/> New SpO ₂ is more than 80-STOP ? <input type="checkbox"/> New FEV ₁ is more than 80-STOP ? <input type="checkbox"/> NO to either <input type="checkbox"/> YES to both
F	Follow steps 3-8 on the right. Instruct patient to inhale contents of 4 capsules, one capsule at a time. Open inhaler, CONFIRM powder has been inhaled.	Record new SpO ₂ and new FEV ₁ . SpO ₂ : _____ % FEV ₁ : _____ L Are both of the following true? <input type="checkbox"/> New SpO ₂ is more than 80-STOP ? <input type="checkbox"/> New FEV ₁ is more than 80-STOP ? <input type="checkbox"/> NO to either <input type="checkbox"/> YES to both

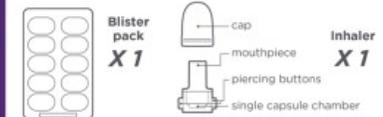
The patient has passed the BTT. BRONCHITOL may be prescribed.

The recommended dosage of BRONCHITOL is 400 mg twice a day. This requires the inhalation of the contents of 10 capsules (blister pack x 1) twice a day.

STOP The patient has failed the BTT. DO NOT continue the BTT. DO NOT prescribe BRONCHITOL.

Wait 15 minutes, then monitor SpO₂ and FEV₁ to confirm recovery to baseline. Treat bronchospasm as needed.

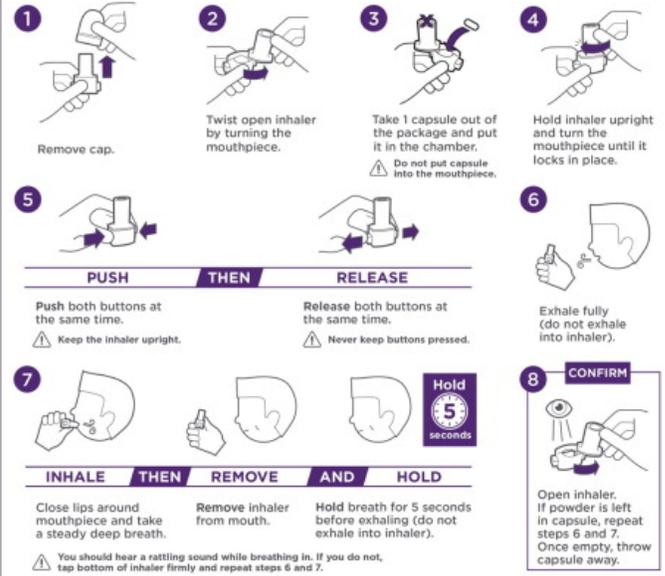
BRONCHITOL Tolerance Test carton includes:



Ensure you have ready

- BRONCHITOL Tolerance Test carton
- Bronchodilator (and spacer if needed)
- Timer
- Spirometer and nose clip
- Pulse oximeter
- Calculator
- Rescue medication and resuscitation equipment
- Sink/hand washing station
- Glass of water for patient to sip during BTT, if necessary
- Pen to record values
- Color in capsules to keep track of how many have been administered

Inhaler use steps for inhalation of the contents of a single capsule



This Healthcare Practitioner Instructions for Use was approved by the U.S. Food and Drug Administration, Rev. 10/2020 CTBR-007-0817-00-SPL CSP/881/03

Patient Information BRONCHITOL[®] (BRONK-ih-to) (mannitol) inhalation powder for oral inhalation use

What is BRONCHITOL?

- BRONCHITOL is a prescription medicine that is used along with other therapies to improve lung function in people 18 years of age and older with cystic fibrosis (CF).
- BRONCHITOL is only for adults who have passed the BRONCHITOL Tolerance Test (BTT). **Your first dose of BRONCHITOL is given during the BTT by your healthcare provider** and tests if BRONCHITOL is right for you. Your healthcare provider will use equipment to monitor you and have medicine ready if you have bronchospasms during the test. If you have bronchospasms during your BTT, then you should not be prescribed BRONCHITOL.

BRONCHITOL should not be used in children and adolescents. It is not known if BRONCHITOL is safe and effective in children under 18 years of age.

Do not take BRONCHITOL if you:

- have had an allergic reaction to mannitol or any parts of the BRONCHITOL capsule. See the end of this Patient Information leaflet for a complete list of ingredients in BRONCHITOL.
- do not pass the BTT.

Before you use BRONCHITOL, tell your healthcare provider about all your

medical conditions, including if you:

- have ever coughed up blood or had blood in your mucus (sputum).
- are pregnant or planning on becoming pregnant. It is not known if BRONCHITOL will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while using BRONCHITOL.
- are breastfeeding or plan to breastfeed. It is not known if BRONCHITOL passes into your breast milk or if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby while using BRONCHITOL.

Tell your healthcare provider about all medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of the medicines you take and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use BRONCHITOL?

See the step-by-step Patient Instructions for Use at the end of this Patient Information leaflet.

- **BRONCHITOL is for oral inhalation only.**
- **Do not** use BRONCHITOL until your healthcare provider has given you the BTT and approved you for treatment. Ask your healthcare provider or pharmacist if you have any questions.
- Use BRONCHITOL exactly as your healthcare provider tells you to use it.
- **Do not** swallow BRONCHITOL capsules. BRONCHITOL capsules should be used only with the provided inhaler device.
- An inhaled short-acting bronchodilator should be used 5 to 15 minutes before **every dose** of BRONCHITOL.
- Use BRONCHITOL **2 times** each day. Breathe in (inhale) through your mouth (oral inhalation) the capsule contents in 10 single BRONCHITOL capsules using the BRONCHITOL inhaler:
 - **1 time in the morning**
 - **1 time at least 2 to 3 hours before bedtime**
- If you use too much BRONCHITOL, call your healthcare provider or go to the nearest emergency room right away if you have any unusual symptoms, such as feelings that you cannot breathe, have wheezing, or cough a lot.
- Do not stop using BRONCHITOL or any other medicines unless told to do so by your healthcare provider because your symptoms might get worse.
- Your healthcare provider may change your medicines as needed.

Call your healthcare provider or get emergency medical care right away if your breathing problems get worse while taking BRONCHITOL.

What are the possible side effects of BRONCHITOL?

BRONCHITOL may cause serious side effects, including:

- **sudden breathing problems immediately after inhaling your medicine.** Use your short-acting bronchodilator or rescue medicine if you have sudden breathing problems. Get emergency medical care right away if your bronchodilator or rescue medicine does not relieve the symptoms.
- **coughing up of blood (hemoptysis).** This is a serious but common side effect. Coughing up blood in your mucus can happen while you are using BRONCHITOL. **Call your healthcare provider or get emergency medical care right away if you cough up a large amount of blood.**

The most common side effects of BRONCHITOL include:

- cough
- coughing up of blood
- pain or irritation in the back of your mouth and throat and discomfort when swallowing
- vomiting
- fever
- joint pain
- bacteria in your sputum

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BRONCHITOL. You can ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Chiesi USA, Inc. at 1-888-661-9260.

How should I store BRONCHITOL?

- Store BRONCHITOL at room temperature between 68°F to 77°F (20°C to 25°C).
- If your BRONCHITOL capsules are stored at temperatures more than 86°F (30°C), throw them away.
- Do not freeze BRONCHITOL.
- Do not refrigerate BRONCHITOL.
- Throw away the BRONCHITOL inhaler after 7 days and get a new one.

Keep BRONCHITOL and all medicines out of the reach of children.

General information about the safe and effective use of BRONCHITOL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BRONCHITOL for a condition for which it was not prescribed. Do not give BRONCHITOL to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about BRONCHITOL. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BRONCHITOL that is written for health professionals.

What are the ingredients in BRONCHITOL?

Active ingredient: mannitol

Inactive ingredients: There are no inactive ingredients in BRONCHITOL.

Capsules: gelatin and water. The imprinting ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide E172.

Manufactured by:

Pharmaxis Ltd
20 Rodborough Road
Frenchs Forest NSW
2086 AUSTRALIA

Manufactured for:

Chiesi USA, Inc.
Cary, NC 27518

USA

1-888-661-9260

BRONCHITOL is registered in the US Patent and Trademark Office.

All trademarks referenced herein are the property of their prospective owners.

For more information about BRONCHITOL or how to use your inhaler, call 1-888-661-9260.

This Patient Information has been approved by the U.S. Food and Drug Administration

1/2024

PATIENT INSTRUCTIONS FOR USE
BRONCHITOL®
(mannitol) inhalation powder
for oral inhalation use

This Patient Instructions for Use contains information on how to take **BRONCHITOL**.

Each BRONCHITOL box contains:

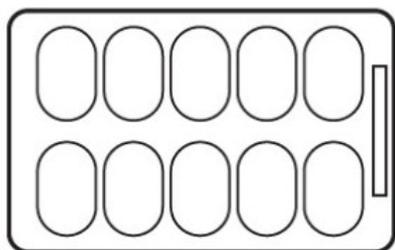
7-Day Treatment Pack

- 140 Capsules (14 blister packs)
- 1 Inhaler
- Prescribing Information

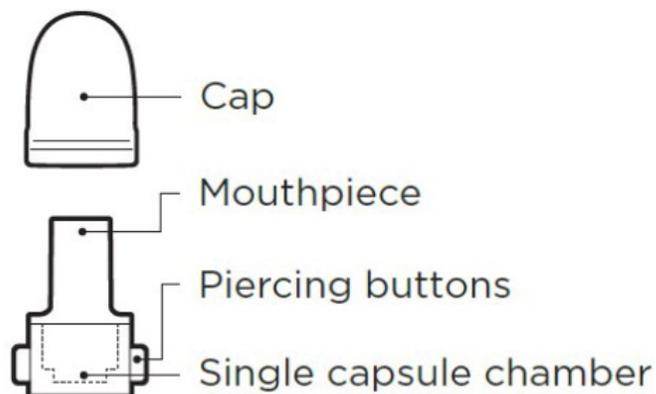
4-Week Treatment Pack

- 560 Capsules (56 blister packs)
- 4 Inhalers
- Prescribing Information

Blister Pack



Inhaler



Important Information You Need to Know Before Using BRONCHITOL

- **Do not use BRONCHITOL until your healthcare provider has performed the BRONCHITOL Tolerance Test (BTT) and approved you for treatment.** This is to make sure you get the right treatment if you have a severe reaction.
- **For oral inhalation only**
- **Do not** swallow BRONCHITOL capsules.
- Use an inhaled short-acting bronchodilator 5 to 15 minutes before every dose of BRONCHITOL
- Use BRONCHITOL **2 times** each day. Inhale through your mouth (oral inhalation) the capsule contents in 10 single BRONCHITOL capsules:
 - **1 time in the morning**

- **1 time at least 2 to 3 hours before bedtime**

Preparing to use BRONCHITOL

BRONCHITOL is supplied to people in cartons containing 140 or 560 capsules in blister packs.

Supplies you will need to use BRONCHITOL:

- 1 Blister pack
- 1 Inhaler
- Bronchodilator (and spacer for bronchodilator if needed)
- Sink or hand washing station

Before using BRONCHITOL:

Use an inhaled bronchodilator 5 to 15 minutes before using BRONCHITOL (See **Figure A**).



Figure A

Clean and dry hands well (See **Figure B**).



Figure B

Inhaler use steps for inhalation of the contents of a single capsule:

Step 1. Remove cap (See **Figure C**)

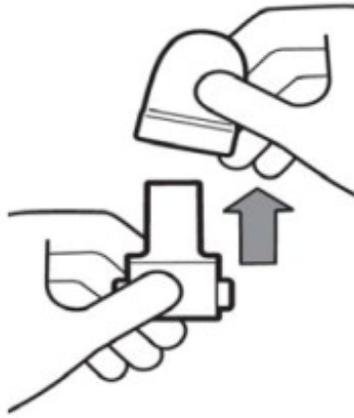


Figure C

Step 2. Twist open inhaler by turning the mouthpiece to the right. (See **Figure D**).

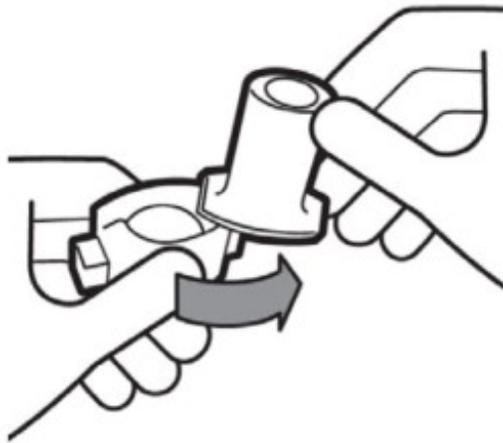


Figure D

Step 3. Take 1 capsule out of the blister pack and put it in the chamber. (See **Figure E**).
Do not place capsule into the mouthpiece of the inhaler.



Figure E

Step 4. Hold inhaler upright and turn the mouthpiece to the left until it locks in place. (See **Figure F**).



Figure F

Step 5. Push both piercing buttons at the same time. Release both piercing buttons at the same time (See **Figure G**).
Keep inhaler upright. Never keep piercing buttons pressed.

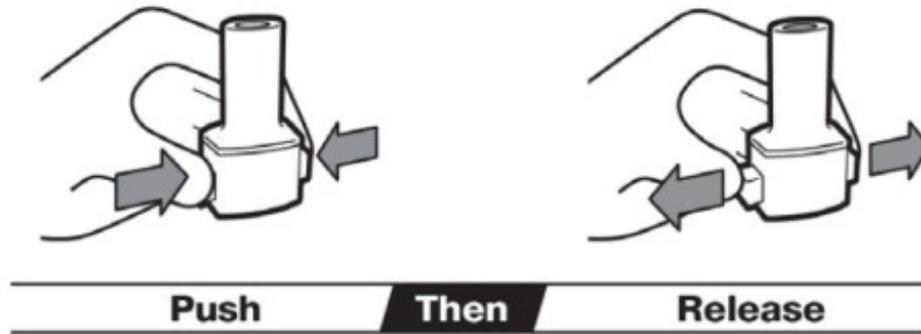


Figure G

Step 6. Breathe out (exhale) fully (See **Figure H**).
Do not breathe out into inhaler.

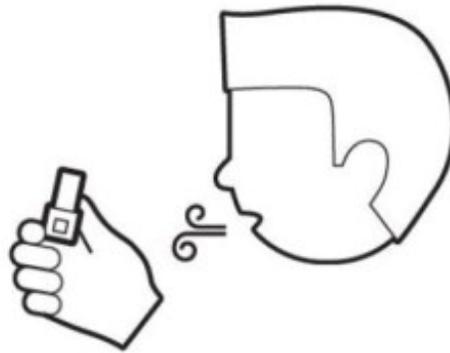


Figure H

Step 7. Close lips around the mouthpiece and take a steady deep breath in through your mouth. **Do not** breathe through your nose. Remove inhaler from mouth. Hold breath for 5 seconds before exhaling, do not breathe out (exhale) into inhaler (See **Figure I**).

You should hear a rattling sound while breathing in. If you do not, tap bottom of inhaler firmly and repeat steps 6 and 7.

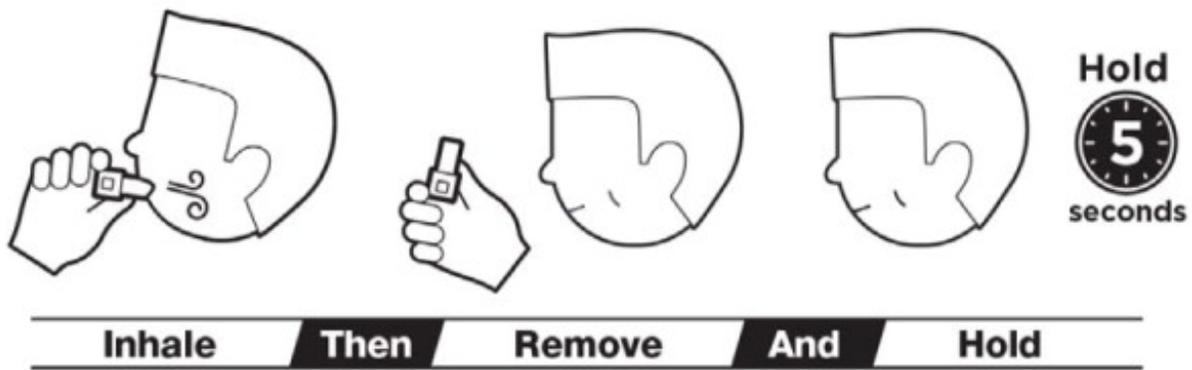


Figure I

Step 8. Open the inhaler by turning the cap to the right. If powder is left in capsule, repeat steps 6 and 7. After the capsule is empty, throw away. (See **Figure J**).



Figure J

Step 9. Repeat steps 3 to 8 for all 10 capsules in 1 blister pack (See **Figure K**).

Breathe in (inhale) contents of each capsule one after another until all 10 capsules in the blister pack are used.

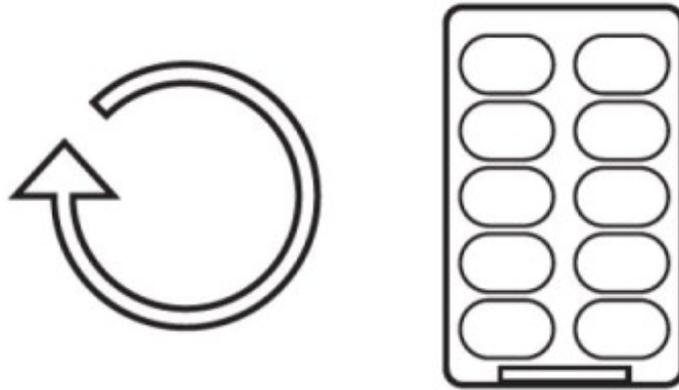


Figure K

Step 10. After inhaling contents of all 10 capsules, close mouthpiece and place cap on inhaler (See **Figure L**).

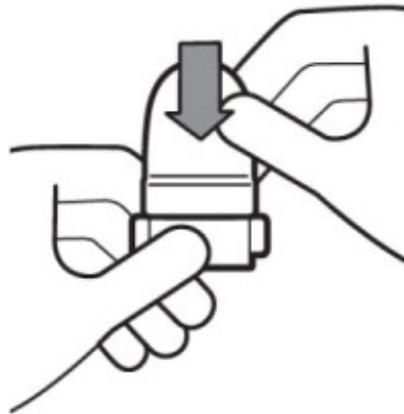


Figure L

Step 11. Continue using BRONCHITOL for 7 days then throw away (discard) the inhaler (See **Figure M**).

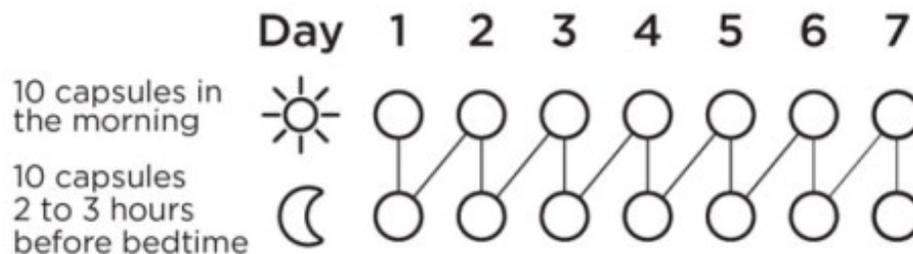


Figure M

How should I store BRONCHITOL?

- Store BRONCHITOL at room temperature between 68°F to 77°F (20°C to 25°C).
- If your BRONCHITOL capsules are stored at temperatures more than 86°F (30°C),

throw them away.

- Do not freeze BRONCHITOL.
- Do not refrigerate BRONCHITOL.
- **Keep BRONCHITOL and all medicines out of the reach of children.**

Cleaning your BRONCHITOL inhaler.

- Your inhaler should give you the correct dose of medicine for 7 days without needing cleaning. However, if your inhaler does need cleaning:
 - Make sure your inhaler is empty.
 - Wash your inhaler in warm water with the mouthpiece open.
 - Shake it until there are no large water droplets left in the inhaler.
 - Leave it to dry in the air by laying it on its side with the mouthpiece open.
 - Allow the inhaler to dry fully (or completely) after it has been washed.

Caring for your BRONCHITOL inhaler.

- Keep your inhaler dry and always make sure your hands are completely dry before using it.
- **Do not** breathe or cough into your inhaler.
- **Do not** take your inhaler apart.
- **Do not** place a capsule directly into the mouthpiece of your inhaler.
- **Do not** leave a used capsule in your inhaler chamber.
- Use a new inhaler after 7 days.
- If your inhaler breaks, call to your healthcare provider.

For more information about BRONCHITOL or how to use your inhaler, call 1-888-661-9260.

Manufactured by:

Pharmaxis Ltd
20 Rodborough Road
Frenchs Forest NSW
2086 AUSTRALIA

Manufactured for:

Chiesi USA, Inc.
Cary, NC 27518
USA

1-888-661-9260

BRONCHITOL is registered in the US Patent and Trademark Office.

This Patient Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 1/2024

CTBR-009-0817-00-SPL-1

Principal Display Panel - 40 mg 4 Week Carton Label

Rx Only

NDC 10122-212-56

Caution: Federal Law Prohibits Dispensing Without A Prescription

Bronchitol®

(mannitol) inhalation powder

40 mg per capsule

FOR ORAL INHALATION ONLY

Do Not Swallow Bronchitol Capsules

Complete entire package (56 Blister Packs) for 28 days treatment

Contents:

56 Blister Cards: 560 capsules (40 mg each)

4 Bronchitol devices: For use with enclosed capsules only

See package insert for complete dosage information

For more information, call 1-888-661-9260.



Complete entire package (56 Blister Packs) for 28 days treatment

Bronchitol[®]
(mannitol) inhalation powder
40 mg per capsule
FOR ORAL INHALATION ONLY

For Single Patient Use Only
Discard After Use
Use As Directed By Your Doctor

FOR ORAL INHALATION ONLY

Store at controlled room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between
15°C - 30°C (59°F - 86°F).

Do not remove capsules from blister until immediately before use.

Keep all medicines out of reach of children.

Manufactured for:
Chiesi USA, Inc.
175 Regency Woods Place,
Suite 600,
Cary, NC 27518

Manufactured by:
Pharmaxis Ltd
20 Rodborough Road,
Fransis Forest, NSW 2096
Australia

Bronchitol[®] is a registered trademark of Pharmaxis Ltd.
CTBR-003-0015-00



10122-212-56 5



Bronchitol[®]
(mannitol) inhalation powder
40 mg per capsule
FOR ORAL INHALATION ONLY



CS187503

Rx Only

Caution: Federal Law Prohibits Dispensing Without A Prescription

NDC 10122-212-56

Bronchitol[®]
(mannitol) inhalation powder
40 mg per capsule
FOR ORAL INHALATION ONLY

Do Not Swallow Bronchitol Capsules

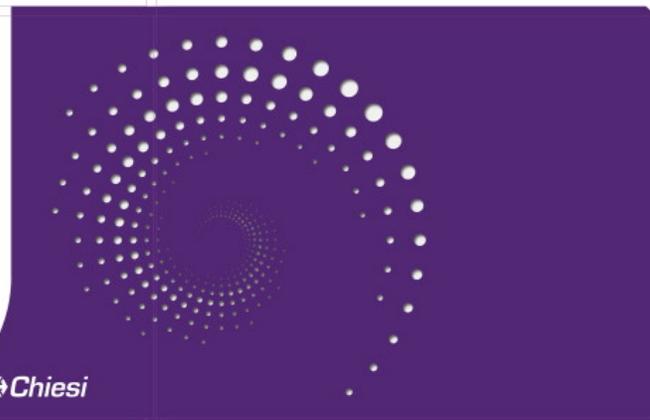
Complete entire package (56 Blister Packs) for 28 days treatment

Contents:

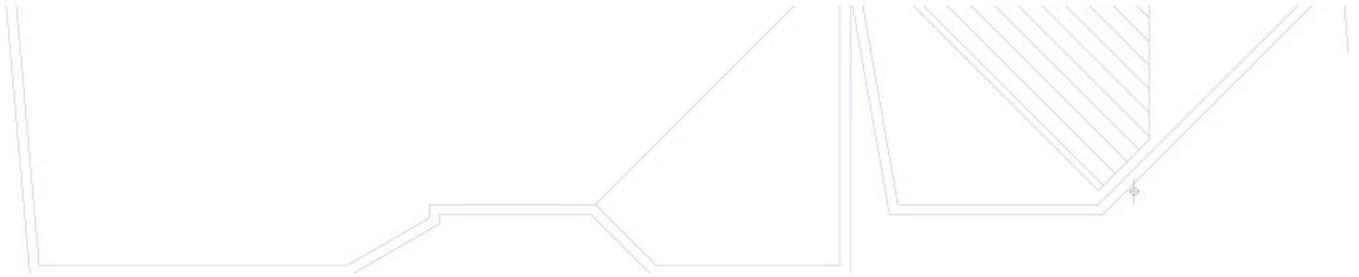
56 Blister Cards: 560 capsules (40 mg each)
4 Bronchitol devices: For use with enclosed capsules only

See package insert for complete dosage information

For more information, call 1-888-661-9260.



HDI



Principal Display Panel - 40 mg 7 Day Carton Label

Rx Only

NDC 10122-212-14

Bronchitol®

(mannitol) inhalation powder

40 mg per capsule

FOR ORAL INHALATION ONLY

Do Not Swallow Bronchitol Capsules

Complete entire package (14 Blister Packs) for 7 days treatment

Contents:

- 14 Blister Packs: 140 capsules (40 mg each)
- 1 Bronchitol inhaler: For use with enclosed capsules only
- Quick reference guide
- Package Insert

See package insert for complete dosage information

For more information, call 1-888-661-9260.



Principal Display Panel - 40 mg Tolerance Test Carton Label

Rx Only

NDC 10122-212-02

Bronchitol®

(mannitol) inhalation powder

Tolerance Test

40 mg per capsule

FOR ORAL INHALATION ONLY

Contents:

- 1 Blister Pack: 10 capsules
- 1 Bronchitol inhaler:
For use with enclosed capsules only
- Tolerance Test Instructions
- Package Insert

The Bronchitol Tolerance Test **MUST** be completed to identify bronchial hyperresponsiveness to mannitol prior to prescribing Bronchitol. Read Tolerance Test instructions for detailed procedure.

Do Not Swallow Bronchitol Capsules

Professional Sample - Not for Sale

Chiesi



Principal Display Panel - 40 mg Tolerance Test Carton Label

Rx Only

NDC 10122-212-04

Bronchitol®

(mannitol) inhalation powder

Tolerance Test

40 mg per capsule

FOR ORAL INHALATION ONLY

Contents:

- 1 Blister Pack: 10 capsules
- 1 Bronchitol inhaler:
For use with enclosed capsules only
- Tolerance Test Instructions
- Package Insert

The Bronchitol Tolerance Test **MUST** be completed to identify bronchial hyperresponsiveness to mannitol prior to prescribing Bronchitol. Read Tolerance Test instructions for detailed procedure.

Do Not Swallow Bronchitol Capsules

Chiesi



BRONCHITOL

mannitol capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10122-212
Route of Administration	RESPIRATORY (INHALATION)		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
mannitol (UNII: 3OWL53L36A) (mannitol - UNII:3OWL53L36A)	mannitol	40 mg

Product Characteristics

Color	white (Clear capsule with white powder)	Score	no score
Shape	CAPSULE (CAPSULE)	Size	15mm
Flavor		Imprint Code	PXS;40;mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10122-212-02	1 in 1 CARTON	02/01/2021	
1	NDC:10122-212-01	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:10122-212-04	1 in 1 CARTON	02/01/2021	
2	NDC:10122-212-01	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:10122-212-14	14 in 1 CARTON	02/01/2021	
3	NDC:10122-212-01	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
4	NDC:10122-212-56	4 in 1 BOX	02/01/2021	
4	NDC:10122-212-14	14 in 1 CARTON		
4	NDC:10122-212-01	10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202049	02/01/2021	09/30/2025

Labeler - Chiesi USA, Inc. (088084228)

Revised: 1/2024

Chiesi USA, Inc.