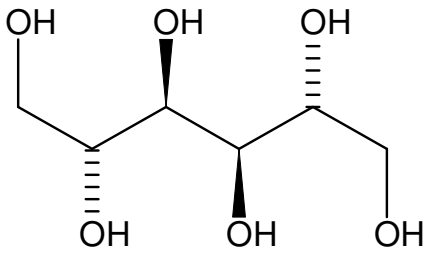
PRODUCT INFORMATION

BRONCHITOL
Mannitol powder for inhalation

Name of the Medicine

Mannitol. Also known as D-mannitol.
The empirical formula is $C_6H_{14}O_6$. Molecular weight is 182.2
CAS number: 69-65-8.

Structural Formula:



Description

Mannitol is a hexahydric alcohol. The powder is a white or almost white, crystalline powder of free-flowing granules. Mannitol is freely soluble in water, and very slightly soluble in alcohol. Mannitol shows polymorphism.

Mannitol is the only ingredient in the contents of the hard gelatin capsules.

Pharmacology

Pharmacodynamics

Bronchitol contains mannitol that has been spray dried to achieve a respirable form. The spray dried mannitol is to be delivered by use of a specific inhaler device. The inhalation of mannitol is intended to improve lung hygiene by correcting the impaired mucociliary clearance that is characteristic of cystic fibrosis. While the exact mechanism of action is unknown, inhaled mannitol may change the viscoelastic properties of mucus, increase the hydration of the periciliary fluid layer and contribute to increased mucociliary and cough clearance of the retained secretions.

Pharmacokinetics

Absorption:
In a study of 18 healthy male adult volunteers, using an Aridol inhaler, the absolute bioavailability of mannitol powder for inhalation by comparison to mannitol administered intravenously was 0.59 ± 0.15. The rate and extent of absorption of mannitol after inhaled administration was very similar to that observed after oral administration. The T_{max} after inhaled administration was 1.5 ± 0.5 hours.

In a study of 9 cystic fibrosis patients (6 adults, 3 adolescents), using 400 mg inhaled mannitol as a single dose (Day 1) then twice a day for 7 days (Days 2-7), pharmacokinetic parameters were similar for adults and adolescents, except for a longer average apparent terminal half life for adolescents (Day 1 = 7.29 hr, Day 7 = 6.52 hr) compared with adults (Day 1 = 6.10 hr, Day 7 = 5.42 hr). Overall, the

comparison of AUCs between Day 1 and Day 7 showed a time independence of pharmacokinetics, indicating linearity at the dose level administered in this study.

Metabolism:
Mannitol is metabolised after oral/inhaled administration (by gut microflora), but little metabolism is observed following intravenous administration. A small percentage of systemically absorbed mannitol undergoes hepatic metabolism to glycogen and carbon dioxide. Studies in rats, mice and humans have demonstrated that mannitol has no toxic metabolites. The metabolic pathway of inhaled mannitol was not examined in PK studies.

Distribution:
Lung deposition studies have demonstrated a 24.7% deposition of inhaled mannitol confirming its distribution to the target organ. Nonclinical toxicology studies indicate that mannitol inhaled into the lungs is absorbed into the bloodstream, with the maximum serum concentration being achieved within 1 hour. In a pharmacokinetic study of mannitol in 18 healthy adults, the volume of distribution was 34.3 ± 13.8 L following a 500mg intravenous dose. There is no evidence that mannitol is accumulated in the body, therefore distribution of inhaled mannitol was not examined in PK studies.

Elimination:
The cumulative amount of mannitol filtered into the urine over the 24 hr collection period was similar for inhaled (55%) and oral (54%) mannitol. When administered intravenously, mannitol is eliminated largely unchanged by glomerular filtration and 87% of the dose is excreted in the urine within 24 hours. The mean terminal half-life in adults was approximately 4-5 hours from serum and approximately 3.66 hours from urine.

Clinical Trials

Two Phase-3 randomised controlled trials (DPM-CF-301, DPM-CF-302) have been conducted in patients with cystic fibrosis aged 6 years or older. The characteristics of the trials were as follows: 26 weeks duration, parallel, double blind. Patients were randomised in a 3:2 ratio to either: (1) inhaled mannitol 400mg twice daily or (2) control/placebo (inhaled mannitol 50mg twice daily).

Of the 389 patients enrolled in study DPM-CF-301, 27 (7%) were not randomised because of a failed mannitol tolerance test (MTT); corresponding numbers for DPM-CF-302 were: 14/342 (4%). An additional 4% (n=27) patients from the two studies had an incomplete MTT and were not randomised.

In study DPM-CF-301, of the patients who were randomised, 29 withdrew before they received any study drug (mannitol:15; placebo:14); the corresponding numbers for study DPM-CF-302 were: 13 (mannitol:8; placebo:5).

In study DPM-CF-301, of the patients who received the study drug, 29/177 (16.4%) patients in the mannitol arm withdrew because of an adverse event; the corresponding figure in the placebo arm was 11/118 (9.3%). In study DPM-CF-302, of the patients who received the study drug, 13/184 (7.1%) patients in the mannitol arm withdrew because of an adverse event; the corresponding figure in the placebo arm was 5/121 (4.1%). The most common reasons for withdrawal due to an adverse event were increased cough and haemoptysis.

In study DPM-CF-301, a further 50 (16.9%) patients withdrew consent during the 26-week, randomised phase; the corresponding figures for DPM-CF-302 were: 20 (6.6%).

Table 1 shows the results for the pre-specified primary endpoint (control-subtracted change from baseline in FEV_1).

Table 1. Control-subtracted change in FEV_1 after 26 weeks (ITT population)

	DPM-CF-301			DPM-CF-302		
	N	**FEV_1 (mL) (95% CI)**	**p-value**	**N**	**FEV_1 (mL) (95% CI)**	**p-value**
All ages	295	94.5 (46.2, 142.7)	<0.001	305	54.1 (-2.0, 110.3)	0.059
6-11 years	48	49.1 (-71.3, 169.5)	0.422	59	81.1 (-45.3, 207.6)	0.208
12-17 years	57	78.0 (-28.8, 184.7)	0.151	95	-9.5 (-108.9, 89.9)	0.851
≥18 years	190	108.5 (47.6, 169.4)	<0.001	151	85.9 (4.6, 167.3)	0.038

For dornase alfa users in DPM-CF-301, the control-subtracted change in FEV_1 after 26 weeks was 77.6mL (95% CI 18.2, 137.1); non-users: 89.6mL (95% CI 25.4, 153.8). The corresponding results for DPM-CF-302 were: dornase alfa users: 43.5mL (95% CI -19.8, 106.8); non-users: 86.5mL (95% CI -23.8, 196.8).

The number of study participants with at least one protocol-defined pulmonary exacerbation (≥ 4 symptoms and signs plus IV antibiotics) was (DPM-CF-301): 18.1% in the mannitol group and 28% in the control group; (DPM-CF-302): 15.2% versus 19.0%.

Indications

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above as either an add-on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to dornase alfa.

Contraindications

Hypersensitivity to mannitol or to any of the capsule ingredients.
Bronchial hyperresponsiveness to inhaled mannitol.

Precautions

Haemoptysis:
Haemoptysis has been commonly reported with Bronchitol in clinical studies in CF.
Bronchitol has not been studied in patients with a history of significant episodes of haemoptysis (>60 mL) in the previous 3 months. As a consequence, these patients should be carefully monitored, and Bronchitol should be withheld in the event of massive haemoptysis. A massive/serious haemoptysis is considered to be:

- acute bleeding ≥240 ml in a 24-hour period
- recurrent bleeding ≥100 ml/day over several days

The reinstitution or withholding of Bronchitol following smaller episodes of haemoptysis should be

based on clinical judgment.
Please also refer to the Adverse Effects section.

Asthma:
The efficacy/safety of Bronchitol in patients with asthma has not been formally studied. Patients with asthma must be carefully monitored for worsening signs and symptoms of asthma after the initiation dose of Bronchitol. Patients must be advised to report worsening signs and symptoms of asthma during therapeutic use of Bronchitol to their physician. If there is evidence of therapy induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of Bronchitol outweigh the risks to the patient. Bronchospasm should be treated with a bronchodilator or as medically appropriate.

Hyperresponsiveness to mannitol:
Patients must be monitored for bronchial hyperresponsiveness to inhaled mannitol during their initiation dose assessment before commencing the therapeutic dose regimen of Bronchitol. If the patient is unable to perform spirometry or complete the initiation dose assessment, they must not be prescribed Bronchitol. If the patient is hyperresponsive, they should not be prescribed the therapeutic dose regimen of Bronchitol. The usual precautions regarding bronchial hyperresponsiveness monitoring apply.

Bronchospasm:
Bronchitol may cause bronchoconstriction requiring treatment, even in patients who were not hyperresponsive to the initiation dose of inhaled mannitol. If a therapy induced hyperresponsive reaction is suspected, Bronchitol should be discontinued. All patients should be formally reviewed after approximately six weeks of Bronchitol treatment to assess for signs and symptoms suggestive of drug induced bronchospasm. The initiation dose assessment should be repeated if uncertainty exists.

Cough:
Cough was very commonly reported with use of Bronchitol in clinical studies.
Patients should be trained to practice correct inhaler technique during treatment and advised to report persistent cough with the use of Bronchitol to their physician.

Impaired Lung Function:

Safety and efficacy have not yet been demonstrated in patients with a FEV_1 of less than 30% of predicted. The use of Bronchitol is not recommended in these patients.

Impaired Hepatic / Renal Function
Bronchitol has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available.

Non CF Bronchiectasis:
Efficacy and safety have not been established in non-CF bronchiectasis patients. Therefore, treatment with Bronchitol is not recommended.

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

Use in Pregnancy (Pregnancy Category B2)
Animal reproduction studies have not been carried out with inhaled mannitol. However, studies with orally administered mannitol indicate no teratogenic effects in mice or rats at daily doses up to 1.6g/kg, or in hamsters at 1.2g/kg/day.

As the effects of a possible hyperresponsiveness reaction on the mother and/or the foetus are unknown, caution should be exercised when prescribing Bronchitol to pregnant women. As a precautionary measure**,** it is preferable to avoid the use of Bronchitol during pregnancy.

Use in Lactation
It is unknown whether mannitol is excreted in human breast milk. The excretion of mannitol in milk has not been studied in animals. A decision on whether to continue/discontinue breast feeding or to continue/discontinue therapy with Bronchitol should be made taking into account the benefit of breast-feeding to the child and the benefit of Bronchitol therapy to the woman.

Paediatric use
Bronchitol is not recommended for use in children below 6 years of age due to insufficent data on safety and efficacy.

Use in the Elderly
In Phase 2 and 3 studies the mean patient age was approximately 20 years. The oldest patient from the Phase 3 studies was 56 years of age. No specific dose recommendations for use in the elderly are available.

Carcinogenicity
No evidence of carcinogenicity was observed when dietary mannitol (≤5%) was administered to mice and rats for 2 years. Carcinogenicity studies have not been carried out with inhaled mannitol.

Genotoxicity
No mutagenic or clastogenic effect has been revealed when mannitol was assayed in a standard battery of genotoxicity tests.

Interactions
Bronchitol has been used in clinical studies in conjunction with standard cystic fibrosis therapies such as mucolytics, antibiotics, bronchodilators, pancreatic enzymes, vitamins, inhaled and systemic corticosteroids, and analgesics. However, no formal interaction studies have been conducted.

Effects on Laboratory tests
No effects were observed on haematology, liver function test, or urea and electrolyte parameters.

Adverse Effects

Initiation dose assessment
The most commonly observed adverse reaction associated with the use of Bronchitol during the initiation dose assessment is cough.
The most important adverse reaction associated with the use of Bronchitol during the initiation dose assessment is bronchospasm.

Therapeutic dose regimen
The most commonly observed adverse reaction associated with the use of Bronchitol is cough. Cough which led to cessation of treatment was also commonly experienced.
The most important adverse reaction associated with the use of Bronchitol is haemoptysis.

Table 2: Most Commonly Reported Treatment-Emergent Adverse Events by MedDRA Preferred Term ≥ 2.0% in Any Treatment Group During the Blinded Study Period.

	DPM-CF-301 DB		DPM-CF-302 DB	
Preferred Term	**Mannitol [N=177] %**	**Control [N=118] %**	**Mannitol [N=184] %**	**Control [N=121] %**
Condition aggravated	32.2	35.6	41.3	44.6
Cough	25.4	20.3	15.2	13.2
Headache	21.5	23.7	14.1	18.2
Bacteria sputum identified	18.6	18.6	3.3	4.1
Nasopharyngitis	14.1	14.4	6.0	5.0
Lower respiratory tract infection	8.5	16.9	3.8	3.3
Haemoptysis	11.9	8.5	7.1	2.5
Pharyngolaryngeal pain	13.6	4.2	10.3	10.7
Upper respiratory tract infection	7.9	6.8	5.4	9.1
Abdominal pain upper	6.8	5.9	3.3	5.8
Arthralgia	6.8	5.9	1.1	0.0
Productive cough	6.8	5.9	2.7	1.7
Vomiting	7.3	3.4	4.9	1.7
Back pain	4.0	5.9	1.6	0.8
Abdominal pain	3.4	6.8	7.6	6.6
Toothache	5.1	2.5	1.6	2.5
Constipation	3.4	4.2	0.5	2.5
Diarrhoea	5.1	0.8	4.3	4.1
Pyrexia	4.0	1.7	9.2	10.7
Fungus sputum test positive	3.4	2.5	1.1	0.0
Ear pain	2.8	3.4	2.7	0.0
Nausea	2.3	4.2	1.6	1.7
Chest discomfort	3.4	1.7	1.6	1.7
Tonsillitis	3.4	1.7	0.5	0.8
Fatigue	2.8	2.5	1.6	4.1
Nasal congestion	2.3	3.4	2.2	2.5
Wheezing	2.3	3.4	1.1	0.8
Epistaxis	2.8	1.7	2.7	2.5
Musculoskeletal chest pain	2.8	1.7	1.1	2.5
Rash	2.3	2.5	2.2	1.7
Viral infection	1.7	2.5	0.5	0.0
Malaise	1.7	2.5	1.6	0.0
Oral candidiasis	2.3	1.7	0.0	1.7
Pain in extremity	2.3	1.7	3.3	1.7
Rhinorrhoea	2.3	1.7	1.6	1.7
Asthma	1.1	2.5	0.0	0.8
Influenza like illness	2.3	0.8	2.7	1.7
Insomnia	2.3	0.8	2.2	0.8
Musculoskeletal pain	2.3	0.8	1.6	2.5
Sinus headache	2.3	0.8	-	-
Chest pain (non-cardiac)	0.6	2.5	0.5	0.0
Stomach discomfort	0.6	2.5	0.5	2.5
Viral upper respiratory tract infection	0.0	3.4	0.5	0.0
Rhinitis allergic	0.0	2.5	0.0	0.8
Sinusitis	1.7	0.8	4.3	5.8
Post-tussive vomiting	1.1	0.0	3.3	1.7
Dizziness	1.1	0.8	1.1	4.1

Influenza	1.1	0.8	3.3	4.1
Dysmenorrhoea	1.1	0.0	3.3	0.0

Table 3: Frequency of adverse reactions with Bronchitol on the day of screening

System Organ Class	Very Common	Common	Uncommon
Metabolism and nutrition disorders			Dehydration
Respiratory, thoracic and mediastinal disorders		Cough	Bronchospasm
Gastrointestinal disorders			Abdominal pain upper Vomiting Post-tussive vomiting
Investigations			Blood alkaline phosphatase increased

Table 4: Frequency of adverse reactions with Bronchitol during the blinded phases of the two pivotal clinical studies

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		Upper respiratory tract infection* Bacterial disease carrier	Oral candidiasis* Staphylococcal infection Bronchitis* Bronchopneumonia Lower respiratory tract infection* Lung infection Pharyngitis* Pneumonia bacterial* Upper respiratory tract infection*
Metabolism and nutrition disorders		Decreased appetite	Cystic fibrosis related diabetes* Polydipsia
Nervous system disorders		Headache	Dizziness
Ear and labyrinth disorders			Ear Pain
Respiratory, thoracic and mediastinal disorders	Cough	Haemoptysis Bronchospasm Wheezing Asthma* Condition aggravated Pharyngolaryngeal pain Productive cough Chest discomfort Throat irritation Bacteria sputum identified*	Respiratory tract congestion Rhinorrhoea Dysphonia Dyspnoea Hyperventilation Obstructive airways disorder Pulmonary congestion Sputum discoloured Vocal chord disorder
Gastrointestinal disorders		Vomiting Post-tussive vomiting	Gastrooesophageal reflux disease Glossodynia Eructation Flatulence Nausea Retching Stomatitis
Skin and subcutaneous tissue disorders			Acne Pruritus Rash Cold sweat Photosensitivity reaction* Rash pruritic

Musculoskeletal and connective tissue disorders			Arthralgia Joint stiffness Musculoskeletal chest pain Musculoskeletal pain Back pain
Renal and urinary disorders			Urinary incontinence Polyuria*
General disorders and administration site conditions Injury, poisoning and procedural complications Investigations Psychiatric disorders			Hernia pain Fatigue Influenza like illness* Malaise Pyrexia Clavicle fracture Bacteria sputum identified Fungus sputum test positive Initial insomnia Morbid thoughts

*Frequency of adverse reaction lower than noted in the control group

Haemoptysis:

An important adverse event associated with the use of Bronchitol is haemoptysis (Table 5). From the pooled data from the two randomised controlled trials, haemoptysis (reported as an adverse event) occurred in 9.4% of patients in the Bronchitol arm versus 5.4% in the control arm. The percentages stratified by age were (Bronchitol versus control): 6-11 years (6.1% versus 0.0%); 12-17 years (9.1% versus 3.1%); ≥18 years (10.6% versus 8.2%).

Table 5 - Haemoptysis events by Age during the Double-Blind Phase of the two pivotal studies (Safety Population)

	Mannitol n (%)	**Control n (%)**
All subjects	**N=361**	**N=239**
Total Haemoptysis reported	48 (13.3)	32 (13.4)
Reported as part of a pulmonary exacerbation (not as an AE)	14 (3.9)	19 (7.9)
Reported as Haemoptysis AE	34 (9.4)	13 (5.4)
Severe	4 (1.1)	1 (0.4)
Related	20 (5.5)	4 (1.7)
Serious	8 (2.2)	2 (0.8)
Study withdrawal	6 (1.7)	0 (0.0)
Pediatric (6-11 yrs)	**N=66**	**N=41**
Total Haemoptysis reported	4 (6.1)	1 (2.4)
Reported as part of a pulmonary exacerbation (not as an AE)	0 (0.0)	1 (2.4)
Reported as AE	4 (6.1)	0 (0.0)
Severe	1 (1.5)	0 (0.0)
Related	2 (3.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)
Study withdrawal	0 (0.0)	0 (0.0)
Adolescent (12-17 yrs)	**N=88**	**N=64**
Total Haemoptysis reported	12 (13.6)	7 (10.9)
Reported as part of a pulmonary exacerbation (not as an AE)	4 (4.5)	5 (7.8)
Reported as AE	8 (9.1)	2 (3.1)
Severe	1 (1.1)	0 (0.0)
Related	6 (6.8)	0 (0.0)
Serious	3 (3.4)	1 (1.6)
Study withdrawal	0 (0.0)	0 (0.0)
Adult (≥18 yrs)	**N=207**	**N=134**
Total Haemoptysis reported	32 (15.5)	24 (17.9)
Reported as part of a pulmonary exacerbation (not as an AE)	10 (4.8)	13 (9.7)
Reported as AE	22 (10.6)	11 (8.2)
Severe	2 (1.0)	1 (0.7)
Related	12 (5.8)	4 (3.0)
Serious	5 (2.4)	1 (0.7)
Study withdrawal	6 (2.9)	0 (0.0)

Cough:

Cough is a very commonly reported AE. Although reported as a common AE, productive cough is a beneficial component of mucus clearance.

Dosage and Administration

Before commencing treatment with Bronchitol, all patients should be assessed for bronchial hyperresponsiveness to inhaled mannitol during administration of their initiation dose (see **Contraindications**). Patients who are contraindicated for spirometry and cannot therefore undergo the initiation dose assessment must not be prescribed Bronchitol.

Initiation Dose Assessment:

The patient's initiation dose of Bronchitol (400 mg) must be used under the supervision and monitoring of an experienced physician or another health professional appropriately trained and equipped to monitor oxygen saturation (SpO_2), perform spirometry and manage acute bronchospasm, including appropriate use of resuscitation equipment.

The patient should be pre-medicated with a bronchodilator 5–15 minutes prior to the initiation dose but after the baseline FEV_1 and SpO_2 measurement. All FEV_1 measurements and SpO_2 monitoring should be performed 60 seconds after dose inhalation.

The initiation dose assessment must be performed according to the following steps:

Step 1: Patients baseline FEV_1 and SpO_2 is measured prior to the initiation dose
Step 2: Patient inhales 40 mg (1x40 mg capsules) and SpO_2 is monitored
Step 3: Patient inhales 80 mg (2x40 mg capsules) and SpO_2 is monitored
Step 4: Patient inhales 120 mg (3x40 mg capsules), FEV_1 is measured and SpO_2 is monitored
Step 5: Patient inhales 160 mg (4x40 mg capsules), FEV_1 is measured and SpO_2 is monitored
Step 6: Patients FEV_1 is measured 15 minutes post initiation dose.

Training the patient to practice correct inhaler technique during this initiation dose assessment is important.

Each of the capsules is loaded into the device separately. The contents of the capsule are inhaled via the inhaler device with one or two breaths. After inhalation, each empty capsule is discarded before inserting the next capsule into the inhaler device.

A patient is defined as hyperresponsive to mannitol and must not be prescribed the therapeutic dose regimen if they experience any of the following:

- $\geq$10% fall in SpO_2 at any point of the assessment
- FEV_1 fall is $\geq$20% at 240 mg cumulative dose
- FEV_1 has fallen $\geq$20% (from baseline) at the end of the assessment and does not return to within <20% of baseline, within 15 minutes.
- FEV_1 has fallen $\geq$50% (from baseline) at the end of the assessment.

All patients should be monitored until their FEV_1 has returned to baseline levels.

Therapeutic Dose Regimen:

The therapeutic dose regimen should not be prescribed until the initiation dose assessment has been

performed.

The recommended dosage of Bronchitol is 400 mg twice a day.
This requires the inhalation of the contents of 10 x 40 mg capsules via the inhaler device, twice a day. Each capsule delivers a dose of approximately 32 mg. The doses should be taken morning and night with the evening dose taken 2-3 hours before bedtime.

The inhaler device is to be replaced after one week of use. If the inhaler does require cleaning, ensure the device is empty then wash in warm water and before re-use, allow the inhaler to thoroughly air dry.
A bronchodilator must be administered 5-15 minutes before Bronchitol is used. The recommended order of treatment is: bronchodilator, Bronchitol, physiotherapy / exercise, then dornase alfa (if applicable).

Overdosage

Incidences of overdose were not observed in the clinical studies. Susceptible persons may suffer bronchoconstriction in the event of an inhaled overdose. If excessive coughing and bronchoconstriction occurs, a β_2 agonist should be given, and oxygen if necessary.

Presentation and Storage Conditions

Bronchitol 40 mg capsules are presented in double aluminium blisters in cartons containing 10, 140 or 280 capsules for initial dose and chronic use respectively. The capsules are clear and imprinted with "**PXS 40 mg**".
The initiation dose carton contains 1 blister strip (of 10 capsules) and one inhaler device.
The 7 day carton contains 14 blister strips (of 10 capsules each) and one inhaler device.
The 14 day carton contains 28 blister strips (of 10 capsules each) and two inhaler devices.
Store below 30°C.

Name and Address of the Sponsor

Pharmaxis Ltd.
20 Rodborough Road
Frenchs Forest NSW 2086
AUSTRALIA

Poison Schedule of the Medicine

Mannitol is Unscheduled.

Date of Approval

07 February 2011.
Date of most recent amendment: 8 October 2015.