AUSTRALIAN PRODUCT INFORMATION – BRONCHITOL (MANNITOL) POWDER FOR INHALATION IN HARD CAPSULES

1 NAME OF THE MEDICINE

Mannitol.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bronchitol contains 40 mg of mannitol.

For the full list of excipients, see *section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

Powder for inhalation in hard capsules.

White powder in a clear hard capsule and imprinted with "PXS 40 mg".

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Before commencing treatment with Bronchitol, all patients should be assessed for bronchial hyperresponsiveness to inhaled mannitol during administration of their initiation dose (see *section 4.3 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: Patient's baseline FEV_1 and SpO_2 are 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: Patient's FEV_1 is measured 15 minutes after last dose.

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

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

- ≥10% fall in SpO_2 at any point of the assessment
- FEV_1 fall is ≥20% at 240 mg cumulative dose
- FEV_1 has fallen ≥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 ≥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 patient must complete and pass the initiation dose assessment before starting treatment with Bronchitol.

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.

Method of administration:
Bronchitol is for inhalation use, using the inhaler provided in the pack. It must not be administered by any other route or using any other inhaler. The capsules must not be swallowed.

Each of the capsules is loaded into the device separately. The contents of the capsules 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.

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), inhaled antibiotics (if applicable).

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 *section 4.8 Adverse Effects (Undesirable Effects)*.)

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 patients are unable to perform spirometry or complete the initiation dose assessment, they must not be prescribed Bronchitol. If patients are hyperresponsive, they should not be prescribed the therapeutic dose regimen of Bronchitol. The usual precautions regarding bronchial hyperresponsiveness monitoring apply. If a therapy induced hyperresponsive reaction is suspected, Bronchitol should be discontinued.

Bronchospasm:
Bronchitol may cause bronchoconstriction/ bronchospasm requiring treatment, even in patients who were not hyperresponsive to the initiation dose of inhaled mannitol. Bronchospasm should be treated with a bronchodilator or as medically appropriate.

If there is evidence of therapy induced bronchospasm, the physician should carefully evaluate the benefits of continued use of Bronchitol outweigh the risks to the patient.

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 commonly reported with use of Bronchitol in clinical studies.

Productive cough may be a beneficial component of mucus clearance.

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.

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

Use in hepatic impairment
Bronchitol has not formally been studied in patients with impaired hepatic function. No specific dose recommendations for this patient population are available.

Use in renal impairment
Bronchitol has not formally been studied in patients with impaired renal function. No specific dose recommendations for this patient population are available.

Use in the elderly
In Phase 2 and 3 studies the mean patient age was approximately 22 years. The oldest patient from the Phase 3 studies was 78 years of age. No specific dose recommendations for use in the elderly are available.

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

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 1 provides a summary of the most commonly reported treatment-emergent adverse events from Phase 3 clinical studies.

Table 1: 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		DPM-CF-303 DB	
Preferred Term	**Mannitol [N=177] %**	**Control [N=118] %**	**Mannitol [N=184] %**	**Control [N=121] %**	**Mannitol [N=207] %**	**Control [N=213] %**
Infection and infestations						
Upper respiratory tract infection	7.9	6.8	5.4	9.1	7.2	5.2
Nasopharyngitis	14.1	14.4	6.0	5.0	5.8	4.7
Viral upper respiratory tract infection	0.0	3.4	0.5	0.0	4.8	2.8
Sinusitis	1.7	0.8	4.3	5.8	2.4	4.2
Rhinitis	0.0	0.0	3.3	0.8	3.9	1.9
Bronchitis	0.0	0.0	3.8	4.1	2.4	1.4
Pharyngitis	0.0	1.7	3.8	1.7	2.4	1.4
Influenza	1.1	0.8	3.3	4.1	1.4	2.3
Lower respiratory tract infection	8.5	16.9	3.8	3.3	1.0	0.5
Oral candidiasis	2.3	1.7	0.0	1.7	0.5	0.9
Tonsillitis	3.4	1.7	0.5	0.8	0	0.5
Viral infection	1.7	2.5	0.5	0.0	0.5	0.5
General disorders and administration site conditions						
Condition aggravated	32.2	35.6	41.3	44.6	27.1	27.7
Pyrexia	4.0	1.7	9.2	10.7	6.3	3.8
Chest discomfort	3.4	1.7	1.6	1.7	2.9	3.3
Fatigue	2.8	2.5	1.6	4.1	1.0	2.3
Malaise	1.7	2.5	1.6	0.0	1.4	0.5
Influenza like illness	2.3	0.8	2.7	1.7	0.5	0

Preferred Term	DPM-CF-301 DB		DPM-CF-302 DB		DPM-CF-303 DB	
	Mannitol [N=177] %	Control [N=118] %	Mannitol [N=184] %	Control [N=121] %	Mannitol [N=207] %	Control [N=213] %
Chest pain (non-cardiac)	0.6	2.5	0.5	0.0	0.5	1.9
Respiratory, thoracic and mediastinal disorders						
Cough	25.4	20.3	15.2	13.2	11.1	9.9
Haemoptysis	11.9	8.5	7.1	2.5	10.1	10.3
Oropharyngeal pain	13.6	4.2	10.3	10.7	4.3	3.8
Productive cough	6.8	5.9	2.7	1.7	2.9	3.8
Nasal congestion	2.3	3.4	2.2	2.5	2.4	2.3
Wheezing	2.3	3.4	1.1	0.8	2.9	1.9
Sinus congestion	0.0	0.0	0.0	0.0	2.4	0.5
Epistaxis	2.8	1.7	2.7	2.5	0	0.9
Rhinorrhoea	2.3	1.7	1.6	1.7	0.5	1.9
Asthma	1.1	2.5	0.0	0.8	1.0	0.5
Rhinitis allergic	0.0	2.5	0.0	0.8	1.0	0
Nervous system disorders						
Headache	21.5	23.7	14.1	18.2	5.8	10.3
Sinus headache	2.3	0.8	-	-	0.5	0.5
Dizziness	1.1	0.8	1.1	4.1	0	1.9
Musculoskeletal and connective tissues disorders						
Arthralgia	6.8	5.9	1.1	0.0	1.0	1.9
Back pain	4.0	5.9	1.6	0.8	0	1.4
Musculoskeletal chest pain	2.8	1.7	1.1	2.5	0	0.5
Pain in extremity	2.3	1.7	3.3	1.7	0.5	0.5
Musculoskeletal pain	2.3	0.8	1.6	2.5	0	0.5
Investigations						
Bacteria sputum identified	18.6	18.6	3.3	4.1	1.9	1.4
Fungus sputum test positive	3.4	2.5	1.1	0.0	1.0	0
Gastrointestinal disorders						
Abdominal pain	3.4	6.8	7.6	6.6	1.9	3.3
Toothache	5.1	2.5	1.6	2.5	1.4	3.3
Abdominal pain upper	6.8	5.9	3.3	5.8	2.4	2.3
Vomiting	7.3	3.4	4.9	1.7	1.0	0.9
Diarrhoea	5.1	0.8	4.3	4.1	2.9	1.9
Constipation	3.4	4.2	0.5	2.5	1.0	0.9
Nausea	2.3	4.2	1.6	1.7	2.4	2.3
Stomach discomfort	0.6	2.5	0.5	2.5	0	0.5
Post-tussive vomiting	1.1	0.0	3.3	1.7	0.5	0
Ear and labyrinth disorders						
Ear pain	2.8	3.4	2.7	0.0	0.5	0.5
Skin and subcutaneous tissue disorders						
Rash	2.3	2.5	2.2	1.7	1.0	0.9
Psychiatric disorders						
Insomnia	2.3	0.8	2.2	0.8	0.5	1.4
Reproductive system and breast disorders						
Dysmenorrhoea	1.1	0.0	3.3	0.0	0.5	2.8

Frequencies provided in **Table 2** are based on clinical review of the observations on the day of screening and prior to the day of study drug dosing (if any) in patients undertaking the initiation dose assessment in the 3 phase III comparative clinical studies investigating the effect of Bronchitol.

Frequencies are defined as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Table 2 contains a selected list of adverse reactions. Other than asthma, only adverse events reported in >2 patients are included.

Table 2: Frequency of adverse reactions in Patients Taking the Mannitol Tolerance Test (DPM-CF-301, DPM-CF-302, DPM-CF-303)

System Organ Class	Common	Uncommon
Metabolism and nutrition disorders		Dehydration
Nervous system disorders		Headache
Respiratory, thoracic and mediastinal disorders	Cough	Wheezing Bronchospasm Forced expiratory volume decreased Asthma
Gastrointestinal disorders		Abdominal pain upper Vomiting Post-tussive vomiting Nausea
General disorders and administration site conditions		Chest discomfort
Investigations		Blood alkaline phosphate increased
Reactions occurring from day of MTT to day of study drug dosing (if any).		

Post-marketing: Adverse reactions from the initiation dose assessment seen in the post-marketing setting but not observed in the clinical trials include Dyspnoea.

Frequencies provided in Table 3 are based on clinical review of the observations during the treatment phase of 3 phase III comparative clinical trials investigating the effect of Bronchitol.

Table 3: Frequency of adverse reactions with Bronchitol based on pooled data during the blinded phases of the Phase III studies

System Organ Class	Common	Uncommon
Infections and infestations		Oral candidiasis Staphylococcal infection Bronchitis Bronchopneumonia Lower respiratory tract infection Lung infection Pharyngitis Pneumonia bacterial Upper respiratory tract infection Bacterial disease carrier

System Organ Class	Common	Uncommon
		Sinusitis
Metabolism and nutrition disorders		Cystic fibrosis related diabetes Decreased appetite
Nervous system disorders	Headache	Dizziness
Ear and labyrinth disorders		Ear pain
Respiratory, thoracic and mediastinal disorders	Cough Haemoptysis Wheezing Condition aggravated Oropharyngeal pain Chest discomfort	Respiratory tract congestion Rhinorrhoea Dysphonia Dyspnoea Hyperventilation Obstructive airways disorder Sputum discoloured Productive cough Throat irritation Bronchospasm Asthma Laryngospasm Rales Sputum retention
Gastrointestinal disorders	Vomiting Post-tussive vomiting	Gastrooesophageal reflux disease Glossodynia Eructation Flatulence Nausea Retching Stomatitis Gingival ulceration
Skin and subcutaneous tissue disorders		Acne Pruritus Rash Cold sweat Rash pruritic Dermatitis allergic
Musculoskeletal and connective tissue disorders		Arthralgia Joint stiffness Musculoskeletal chest pain Musculoskeletal pain Back pain Temporomandibular joint syndrome
Renal and urinary disorders		Urinary incontinence
General disorders and administration site conditions		Hernia pain Fatigue Influenza like illness Malaise Pyrexia
Injury, poisoning and procedural complications		Clavicle fracture Wrong technique in drug usage process
Investigations		Bacteria sputum identified Fungus sputum test positive
Psychiatric disorders		Initial insomnia Morbid thoughts

Haemoptysis:
An important adverse event associated with the use of Bronchitol is haemoptysis (**Table 4**). From the pooled data from DPM-CF-301 and DPM-CF-302, 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 4: Haemoptysis events by Age during the Double-Blind Phase of the two pivotal studies (DPM-CF-301 & DPM-CF-302) (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)

In DPM-CF-303, the number of patients reporting haemoptysis as a treatment emergent adverse event occurred in 10.1% of patients in the Bronchitol arm versus 10.3% in the control arm.

Cough:
Cough is a commonly reported adverse reaction. Although uncommonly reported as an adverse reaction, productive cough is a beneficial component of mucus clearance.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at *www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
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.

Clinical trials
Three Phase-3 randomised, double-blind, parallel, controlled trials of 26 weeks duration have been conducted in patients with cystic fibrosis. In the DPM-CF-301 and DPM-CF-302 trials, patients aged 6 years or older were randomised in a 3:2 ratio to either: (1) inhaled mannitol 400mg twice daily or (2) control (inhaled mannitol 50mg twice daily). In the third study (DPM-CF-303), 423 adult patients were randomised in a 1:1 ratio to inhaled mannitol 400 mg twice daily or to control.

Enrolled patients who were not randomised because of a failed mannitol tolerance test (MTT) were 27/389 (7%) in study DPF-CF-301, 14/342 (4%) in study DPM-CF-302 and 25/486 (5.1%) in study DPM-CF-303. Additionally, 4% (n=27) patients from the first two studies and 1.4% (7/486) from study DPM-CF-303 had an incomplete MTT and were not randomised.

The number of patients who were randomised but withdrew before they received any study drug was 29 (mannitol:15; control:14) in study DPM-CF-301, 13 (mannitol:8; control:5) in study DPM-CF-302, and 3 (mannitol: 2; control:1) in study DPM-CF-303.

A further 50 (16.9%) patients in study DPM-CF-301, 20 (6.6%) in study DPM-CF-302 and 25 (5.9%) in study DPM-CF-303 withdrew consent during the 26-week, randomised phase.

Of the patients who received the study drug in study DPM-CF-301, 28/177 (15.8%) patients in the mannitol arm and 10/118 (8.5) in the control arm experienced an adverse event leading to study withdrawal. The corresponding numbers in study DPM-CF-302 were 13/184 (7.1%) patients in the mannitol arm and 5/121 (4.1%) in the control arm; and in study DPM-CF-303,

8/207 (3.9%) patients in the mannitol arm and 7/213 (3.3%) in the control arm. The most common adverse events leading to study withdrawal were increased cough, condition aggravated and haemoptysis.

Table 5 shows the results for the pre-specified primary endpoint (control-subtracted change from baseline in FEV_1).

Table 5: Control-subtracted change in FEV_1 after 26 weeks (ITT population)

	DPM-CF-301			DPM-CF-302			DPM-CF-303		
	N	**FEV_1 (mL) (95% CI)**	**p-value**	**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	423	54 (8, 100)	0.020
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	423	54 (8, 100)	0.020
Note: There were some differences in analysis methods across the 3 studies. In DPM-CF-303 imputation of missing data was performed using a baseline observation carried forward imputation using dropout reason approach whereas no imputation was performed in DPM-CF-301 or DPM-CF-302									

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); and for DPM-CF-303: dornase alfa users: 29mL (95% CI -23, 81); non-users: 112 mL (95% CI 22, 202).

The number of study participants with at least one protocol-defined pulmonary exacerbation (≥ 4 symptoms and signs plus IV antibiotics) in DPM-CF-301 was 18.1% in the mannitol group and 28% in the control group; in DPM-CF-302 15.2% versus 19.0%; and in DPM-CF-303, 13.4% versus 13.6%.

5.2 PHARMACOKINETIC PROPERTIES

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.

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.

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.

Excretion
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.

5.3 PRECLINICAL SAFETY DATA

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule shell component: Gelatin.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Bronchitol 40 mg capsules are presented in Aluminium/Aluminium blisters. Each blister strip contains 10 hard capsules.

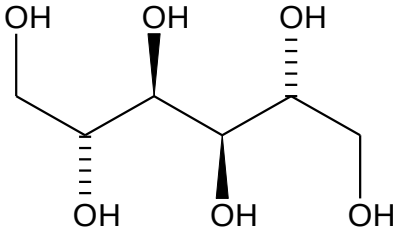
Pack sizes
The initiation pack: cartons containing 1 blister strip and one inhaler device.
The 7 day pack: cartons containing 14 blister strips and one inhaler device.
The 14 day pack: cartons containing 28 blister strips and two inhaler devices.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Also known as D-mannitol. 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.

The empirical formula is $C_6H_{14}O_6$. Molecular weight is 182.2

CAS number
69-65-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Mannitol is Unscheduled.

8 SPONSOR

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Hawthorn Vic 3122
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Website: www.btchealth.com.au
Phone:1800 100 282

9 DATE OF FIRST APPROVAL

07 February 2011

10 DATE OF REVISION

10 June 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Transfer of Sponsor