

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bronchitol 40 mg inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 40 mg mannitol.

Mean delivered dose per capsule is 32.2 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

Clear colourless hard capsules marked with 'PXS 40 mg' and containing white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

4.2 Posology and method of administration

The patient's initiation dose of Bronchitol (400 mg) must be used under the supervision and monitoring of an experienced physician or another health care professional appropriately trained and equipped to perform spirometry, monitor oxygen saturation (SpO₂), and manage acute bronchospasm (see sections 4.4 and 4.8) including appropriate use of resuscitation equipment.

Posology

Initiation dose assessment

Before commencing treatment with Bronchitol, all patients should be assessed for bronchial hyperresponsiveness to inhaled mannitol during administration of their initiation dose (see sections 4.4 and 5.1).

The patient should be pre-medicated with a bronchodilator 5-15 minutes prior to the initiation dose but after the baseline FEV₁ and SpO₂ (Oxygen saturation in the blood) measurement. All FEV₁ measurements and SpO₂ monitoring should be performed 60 seconds after dose inhalation.

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

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

- Step 1: Patients baseline FEV₁ and SpO₂ is measured prior to the initiation dose
- Step 2: Patient inhales 40 mg (1x40 mg capsules) and SpO₂ is monitored
- Step 3: Patient inhales 80 mg (2x40 mg capsules) and SpO₂ is monitored
- Step 4: Patient inhales 120 mg (3x40 mg capsules), FEV₁ is measured and SpO₂ is monitored

Step 5: Patient inhales 160 mg (4x40 mg capsules), FEV₁ is measured and SpO₂ is monitored

Step 6: Patients FEV₁ is measured 15 minutes post initiation dose.

Patients with asthma may experience reversible temporary mild bronchospasm after passing the initiation dose assessment and therefore all patients should be monitored until their FEV₁ 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.

For patients receiving several respiratory therapies, the recommended order is:

1. Bronchodilator
2. Bronchitol
3. Physiotherapy/exercise
4. Dornase alfa (if applicable)
5. Inhaled antibiotics (if applicable)

A bronchodilator must be administered 5-15 minutes before each dose of Bronchitol.

The recommended dose of Bronchitol is 400 mg twice a day. This requires the inhalation of the contents of ten capsules via the inhaler device twice a day.

Special populations

Renal or hepatic impairment

Bronchitol has not specifically been studied in patients with impaired renal and hepatic function. Available data from studies DPM-CF-301 and 302 suggest that no dose adjustments are required for these patient populations.

Elderly patients (≥65 years)

There are insufficient data in this population to support a recommendation for or against dose adjustment.

Paediatric population

The safety and efficacy of Bronchitol in children and adolescents aged 6 to 18 years has not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

The safety and efficacy of Bronchitol in children aged less than 6 years has not been established. No data are available.

Method of administration

Bronchitol is administered by the oral inhalation route 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.

The doses should be taken morning and night with the evening dose taken 2-3 hours before bedtime.

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 with as little delay as possible between capsules.

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.

Detailed instructions on how to use the inhaler can be found in the patient information leaflet. Patients should be advised to carefully read them.

4.3 Contraindications

Hypersensitivity to the active substance.

Bronchial hyperresponsiveness to inhaled mannitol (see section 4.4).

4.4 Special warnings and precautions for use

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. Hyperresponsive patients should not be prescribed the therapeutic dose regimen of Bronchitol (see section 4.3). The usual precautions regarding bronchial hyperresponsiveness monitoring apply (see section 4.2).

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

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

If a therapy induced hyperresponsive reaction is suspected, Bronchitol should be discontinued.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal product and has been reported with Bronchitol in clinical studies, even in patients who were not hyperresponsive to the initiation dose of inhaled mannitol (see section 4.8). Bronchospasm should be treated with a bronchodilator or as medically appropriate.

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.

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 described in section 4.2 should be repeated if uncertainty exists.

Asthma

The safety/efficacy of mannitol in patients with asthma has not been properly 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 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.

Haemoptysis

Haemoptysis has been commonly reported with Bronchitol in clinical studies. Bronchitol has not been studied in patients with a history of significant episodes of haemoptysis (>60 ml) in the previous three 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 reinstatement or withholding of Bronchitol following smaller episodes of haemoptysis should be based on clinical judgement.

Cough

Cough was very commonly reported with use of Bronchitol in clinical studies (see section 4.8).

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 been demonstrated in patients with a FEV₁ of less than 30% of predicted (see section 5.1). 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.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been conducted.

However, Bronchitol has been used in clinical studies in conjunction with standard cystic fibrosis therapies such as mucolytics, antibiotics (including tobramycin and colistimethate sodium), bronchodilators, pancreatic enzymes, vitamins, inhaled and systemic corticosteroids, and analgesics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of mannitol in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As the effects of a possible hyperresponsive reaction on the mother and/or 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.

Breastfeeding

It is unknown whether mannitol is excreted in human milk. The excretion of mannitol in milk has not been studied in animals. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue Bronchitol therapy taking into account the benefit of breast feeding for the child and the benefit of Bronchitol therapy for the woman.

Fertility

For mannitol no clinical data on fertility is available. Animal reproduction studies have not been carried out with inhaled mannitol. However, studies with orally administered mannitol indicate no fertility effects (see section 5.3).

4.7 Effects on ability to drive and use machines

Bronchitol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Initiation dose assessment

The most commonly observed adverse reaction associated with the use of Bronchitol during the initiation dose assessment is cough (3.6% of patients), (see section 4.4).

The most important adverse reaction associated with the use of Bronchitol during the initiation dose assessment is bronchospasm (see section 4.4).

Therapeutic dose regimen

The most commonly observed adverse reaction associated with the use of Bronchitol is cough (see section 4.4). This was observed in 10.2% of patients compared to 5.0% of patients in the control arm. Cough which led to cessation of treatment was also commonly experienced and was observed in 4.7% of patients in the Bronchitol treatment arm.

The most important adverse reaction associated with the use of Bronchitol is haemoptysis. The proportion of patients who experienced haemoptysis as an adverse reaction was 7.3% and 2.9% in the Bronchitol arms for studies 301 and 302, respectively vs. 3.4% and 0% in the control arms. Total haemoptysis incidence including during exacerbation was 15.8% in the mannitol arm and 14.6% in the control arm (see section 4.4).

Tabulated list of adverse reactions

Frequencies provided in Table 1 and 2 are based on the observations on the day of screening and during two pivotal comparative clinical studies investigating the effect of Bronchitol (safety population, 361 patients on Bronchitol).

Frequencies are defined as:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($\geq 1/100,000$ to $< 1/10,000$); Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Frequency of adverse reactions with Bronchitol during the treatment phase and on the day of screening

System organ class	Very common	Common	Uncommon
Infections and infestations			Bacterial disease carrier Oral candidiasis Staphylococcal infection
Metabolism and nutrition disorders			Decreased appetite CF related diabetes Dehydration ¹
Psychiatric Disorders			Initial insomnia Morbid thoughts
Nervous system disorders		Headache	Dizziness ²
Ear and labyrinth disorders			Ear Pain
Respiratory, thoracic and mediastinal disorders	Cough	Haemoptysis Condition aggravated ² Pharyngolaryngeal pain Cough ¹ Chest discomfort ² Wheezing	Wheezing ¹ Bacteria sputum identified Asthma Rhinorrhoea Bronchospasm ²

		Productive cough Throat irritation	Fungus sputum test positive Dysphonia Dyspnoea Hyperventilation Obstructive airways disorder Respiratory tract congestion Sputum discoloured Bronchitis Bronchopneumonia Lung infection Pharyngitis Upper respiratory tract infection Hypoxia ¹ Productive cough ¹ Forced expiratory volume decreased ¹ Chest pain ¹ Throat irritation ¹
Gastrointestinal disorders		Post-tussive vomiting Vomiting	Nausea ² Vomiting ¹ Diarrhoea ¹ Eructation Flatulence Gastrooesophageal reflux disease Glossodynia Retching ² Stomatitis Abdominal pain upper ¹ Apthous Stomatitis ¹ Odynophagia ¹ Post-tussive vomiting ¹
Skin and subcutaneous tissue disorders			Acne Cold sweat Pruritus Rash Rash pruritic
Musculoskeletal and connective tissue disorders			Musculoskeletal chest pain Arthralgia Back pain Joint stiffness Musculoskeletal pain
Renal and urinary disorders			Urinary incontinence
General disorders and administration site conditions			Influenza like illness Fatigue ² Hernia pain Malaise Pyrexia
Investigations			Blood alkaline phosphatase increased ¹

¹Adverse reaction occurred on the day of screening

²Adverse reaction occurred both during the treatment phase and on the day of screening

Twenty seven (7%) out of 389 patients enrolled in study 301 and 14 (4.1%) out of 342 enrolled in study 302 were not randomised due to a positive mannitol tolerance test (MTT). In study 301, overall the most frequently reported events during the MTT were cough in 18 (4.8%) subjects, wheezing/bronchospasm in eight (2.1%) subjects and chest discomfort in six (1.6%) subjects. In study 302 the most frequent clinical sign or symptom reported during the MTT was cough (7.9%).

Paediatric population (6 to 17 years of age)

Frequency, type and severity of adverse reactions in children are similar to those observed in adults.

Initiation dose

The most commonly observed adverse reaction associated with the use of Bronchitol during the initiation dose assessment with the paediatric population is cough (4.8% of patients).

The most important adverse reaction associated with the use of Bronchitol during the initiation dose assessment with the paediatric population is bronchospasm.

Therapeutic dose regimen

The most commonly observed adverse reaction associated with the use of Bronchitol is cough. This was observed in 7.8% of patients compared to 3.8% of patients in the control arm.

The most important adverse reaction associated with the use of Bronchitol is haemoptysis.

Table 2: Frequency of adverse reactions with Bronchitol during the treatment phase and on the day of screening-paediatric population

System organ class	Very common	Common	Uncommon
Psychiatric disorders			Initial insomnia
Nervous system disorders		Headache	Dizziness ²
Ear and labyrinth disorders			Ear Pain
Respiratory, thoracic and mediastinal disorders		Cough ² Condition aggravated Haemoptysis Pharyngolaryngeal pain Bacteria sputum identified Chest discomfort Wheezing Asthma Productive cough	Bronchitis Bronchopneumonia Dysphonia Hyperventilation Sputum Discoloured Throat irritation Pharyngitis Upper respiratory tract infection Bronchospasm ¹ Dyspnoea Chest discomfort ¹ Chest pain ¹
Gastrointestinal disorders		Vomiting Post-tussive vomiting	Nausea ² Vomiting ¹ Odynophagia ¹ Post-tussive vomiting ¹ Retching ¹
Skin and subcutaneous tissue disorders			Pruritus Pruritic rash
Musculoskeletal and connective tissue disorders			Musculoskeletal chest pain
Renal and urinary disorders			Urinary incontinence
General disorders and			Pyrexia

administration site conditions			
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¹Adverse reaction occurred on the day of screening

²Adverse reaction occurred both during the treatment phase and on the day of screening

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V*.

4.9 Overdose

Susceptible persons may suffer bronchoconstriction in the event of an inhaled overdose. If excessive coughing and bronchoconstriction occurs, a beta₂ agonist should be given, and oxygen if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations, Mucolytic. ATC code: R05CB16

Mechanism of action

Bronchitol is an inhaled hyperosmotic medicinal product. 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 mucus clearance of the retained secretions through mucociliary activity. Productive cough can contribute to sputum clearance.

Pharmacodynamic effects

In the ITT population of an open label dose response study, DPM-CF-202, the mean (SD) percent change in FEV₁ for the 400 mg dose was 8.75 (SD: 12.4) and -1.569 (SD: 9.0) for 40 mg dose (p < 0.0001).

Clinical efficacy and safety

Two Phase 3, 26-week double blind, randomised, parallel arm, controlled, intervention studies (DPM-CF-301 and DPM-CF-302) have been performed in which 324 (DPM-CF-301) and 318 (DPM-CF-302) patients aged 6 years and above were randomised in a 3:2 ratio to inhaled mannitol 400 mg twice daily or to control (inhaled mannitol 50 mg twice daily). Twenty seven (7%) out of 389 patients enrolled in study 301 and 14 (4.1%) out of 342 enrolled in study 302 were not randomised due to a positive mannitol tolerance test (MTT) defined as either 1) a fall in FEV₁ >20% from baseline at midpoint (step 4) or 2) fall from baseline > 20 % at end of test that did not recover to < 20% within 15 minutes or 3) who had a fall in FEV₁ > 50% from baseline at end of test (step 6) or 4) who had a fall in SpO₂ to < 89% during the procedure. An additional 4% (n=27) of patients from the two studies had incomplete MTTs and were not randomised.

Mean (SD) baseline FEV₁ percent predicted in study DPM-CF-301 (safety population, N= 295) was 62.4 (SD:16.45) and 61.4 (SD:16.13) in the mannitol and control groups, respectively. These figures for study DPM-CF-302 (N=305) are as follows: 65.24 (SD:13.90) and 64.35 (SD:15.29). In study DPM-CF-301 64.4 % of the patient population were adults while in study DPM-CF-302 this figure was 49.5%. Fifty five % of patients were receiving rhDNase in study DPM-CF-301 while in study DPM-CF-302 this number was 75%. The percentage of patients receiving inhaled antibiotics was 55% in study DPM-CF-301 and 56% in study DPM-CF-302. Concomitant administration with hypertonic saline was not permitted in these trials.

The primary pre-specified endpoint i.e. the change from baseline in FEV₁ (ml) in the modified ITT (mITT) population (n=269 and 297 in studies DPM-CF-301 and DPM-CF-302, respectively)

compared to control over the 26 weeks period is provided in Table 1 alongside FEV₁ presented as absolute and relative change % predicted.

Table 1 – Change in FEV₁ from baseline over 26 weeks in the mITT and adult populations

	Effect size estimate			
	DPM-CF-301		DPM-CF-302	
	FEV ₁ (95% CI)	p value	FEV ₁ (95% CI)	p value
	Overall Population			
	N=269		N=297	
Absolute mL	94.5 (46.2, 142.7)	<0.001	54.1 (-1.97, 110.3)	0.059
Absolute % predicted	2.4 (0.9, 3.9)	0.001	1.9 (-0.02, 3.8)	0.052
Relative % predicted	3.5 (1.0, 6.1)	0.007	3.6 (0.3, 6.9)	0.033
	Adult Population			
	N=171		N=144	
Absolute mL	108.5 (47.6, 169.4)	<0.001	85.9 (4.6, 167.3)	0.038
Absolute % predicted	2.7 (0.9, 4.5)	0.004	2.3 (-0.4, 5.1)	0.095
Relative % predicted	4.3 (1.1, 7.5)	0.008	5.0 (0.2, 9.8)	0.040

In rhDNase users in study 301 the relative change in FEV₁ % predicted from baseline across 26 weeks of treatment was 2.83 (95% CI -0.62, 6.27). For non-users the relative change was 4.30 (95% CI 0.53, 8.07). In study 302 the relative change (95% CI) for rhDNase users and non-users was 3.21 (-0.61, 7.03) and 4.73 (-1.93, 11.40), respectively.

The number of subjects with at least one protocol defined pulmonary exacerbation (PDPE, defined by the presence of at least 4 symptoms and signs plus the use of intravenous antibiotics) was 18.1% in the mannitol arm and 28% in the control arm in study 301 (ITT population). In study 302 15.2% subjects in the mannitol arm and 19% in the control had a PDPE.

The estimated effect of treatment (mean change and 95% CI from baseline over 26 weeks, mITT population) on FVC was 108.78 ml (95% CI: 49.21, 168.35) in study 301 and 71.4 ml (95% CI: 10.57, 132.13) in study 302.

Paediatric population

As stated in section 4.2, the safety and efficacy of Bronchitol in children and adolescents aged less than 18 years has not been established.

In studies DPM-CF-301 and 302 relative % predicted FEV₁ compared to control in children (6-11 years) was improved by 0.44% (95% CI -5.90, 6.77, N=43) and 6.1% (95% CI -1.28, 13.54, N=59) over 26 weeks (p=0.892 and 0.104) respectively.

In adolescents (12-17 years) relative change in % predicted FEV₁ compared to control improved by 3.31% (95% CI -2.29, 8.90, N=55) and 0.42% (95% CI -5.45, 6.29, N=94) over 26 weeks (p=0.245 and 0.888) respectively.

5.2 Pharmacokinetic properties

Absorption

In a study of 18 healthy male adult volunteers, 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 hours, Day 7 = 6.52 hours) compared with adults (Day 1 = 6.10 hours, Day 7 = 5.42 hours). 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.

Biotransformation

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 pharmacokinetic 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 occurring at 1 hour. 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 hour 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 to 5 hours from serum and approximately 3.66 hours from urine.

Paediatric population

The safety and efficacy of Bronchitol in children and adolescents aged 6 to 18 years has not yet been established.

Adolescents aged 12 to 17 years. Limited data available in the population indicate the pharmacokinetic parameters of inhaled mannitol are similar to the adult population. There are no data available for children under 12 years of age.

5.3 Preclinical safety data

In male rats after 13 weeks of inhaled mannitol dosing, elevated circulating lymphocyte numbers and mandibular lymph node plasmacytosis was observed at doses greater than 9.3 fold the maximal dose. The elevated lymphocyte count was within historical control values, did not progress and was essentially resolved by the end of the in life phase of the study and following withdrawal of treatment. This effect was not noted in any other species and did not result in clinical signs.

In dogs an increased occurrence of coughing was observed both during and immediately post dose for low and high dose inhaled mannitol administration. No treatment-related adverse effect occurred greater than 13 fold the maximal therapeutic dose.

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

Mannitol was shown not to be an irritant in an isolated bovine eye assay or when introduced into rabbit eyes.

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

Reproduction and developmental toxicity studies have not been carried out with inhaled mannitol. However, studies conducted with mannitol administered via other routes indicated no effect on foetal survival in mice, rats and hamsters and on embryo and foetal development in rats and rabbits.

Animal reproduction studies have not been carried out with inhaled mannitol. However, studies conducted with orally administered mannitol indicated no teratogenic effects in mice or rats, at doses of up to 1.6 g/kg, or in hamsters at 1.2 g/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Discard the inhaler and its cap 1 week after first use.

6.4 Special precautions for storage

Store below 30°C.

Bronchitol capsules must always be stored in the blister to protect from moisture and only removed immediately before use.

6.5 Nature and contents of container

Bronchitol 40 mg capsules are presented in double aluminium blisters in cartons containing 10 or 280 capsules for initial dose and treatment use respectively.

The initiation dose carton contains 1 blister strip (of 10 capsules) and one inhaler device.

The 2-week carton contains 28 blister strips (of 10 capsules each) and two inhaler devices.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Pharmaxis Pharmaceuticals Limited,
25 Moorgate,
London,
EC2R 6AY
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/760/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13.04.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Mawdsleys Clinical Services,
Unit 22, Quest Park,
Wheatley Hall Road,
Doncaster, DN2 4LT,
United Kingdom

or

Arvato distribution GmbH
Gottlieb-Daimler Straße 1
33428 Harsewinkel
North Rhine-Westphalia
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Bronchitol are provided with an educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a leaflet that includes information on the following key elements:

- The risk of bronchospasm during treatment
 - The need to perform the Bronchitol initiation dose assessment to identify patients who have bronchial hyperresponsiveness in response to inhaled mannitol by measuring the degree of bronchoconstriction that occurs following sequential administrations of mannitol.
 - How to perform the Bronchitol initiation dose assessment safely and how long to monitor the patient for.
 - How to interpret the results of the Bronchitol initiation dose assessment as Pass, Fail or Incomplete.
 - That therapeutic doses of Bronchitol should only be prescribed if the patient has passed the initiation dose assessment.
 - The need of pre-medication by a bronchodilator 5-15 minutes before the Bronchitol initiation dose assessment and before each therapeutic administration of Bronchitol.
 - The need to check that the patient knows how to correctly use the bronchodilator.
 - The need to review the patient after approximately six weeks to assess for signs and symptoms of bronchospasm.
 - The risk of bronchospasm during long term treatment even if the Bronchitol initiation dose assessment was initially passed and the need to reiterate it in case of doubt.
- The risk of haemoptysis during treatment
 - That Bronchitol has not been studied in patients with a history of significant haemoptysis (>60 ml) in the previous three months.
 - The need for monitoring and when to withhold treatment.
- The potential risk of cough related sequelae during treatment
 - The need to train the patient to minimise cough during administration in using the correct inhalation technique.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The applicant is requested to submit periodic analysis of the CF study every 6 months for 3 years and annually for 2 years. The final report is expected in Q1 2018.	Q1 2018

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – INITIATION DOSE PACK

1. NAME OF THE MEDICINAL PRODUCT

Bronchitol 40 mg, inhalation powder, hard capsules
Mannitol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg mannitol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule.

10 hard capsules and 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Initiation dose must be used under medical supervision and include monitoring of lung function.

Use as directed by your doctor.

Refer to package leaflet for inhaler device instructions.

Capsules contain powder for oral inhalation using the inhaler device enclosed.

Do not remove capsules from blister until immediately before use.

Read the package leaflet before use.

Inhalation use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The capsules are not to be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pharmaxis Pharmaceuticals Limited
25 Moorgate
London
EC2R 6AY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/760/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bronchitol 40 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 2-WEEK TREATMENT PACK

1. NAME OF THE MEDICINAL PRODUCT

Bronchitol 40 mg, inhalation powder, hard capsules
Mannitol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg mannitol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule.
2-week treatment pack of 280 hard capsules and 2 inhalers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use as directed by your doctor.

Refer to enclosed leaflet for inhaler device instructions.

Capsules contain powder for oral inhalation using the inhaler device enclosed.

Do not remove capsules from blister until immediately before use.

Read the package leaflet before use.

Inhalation use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The capsules are not to be swallowed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/760/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bronchitol 40 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Bronchitol 40 mg, inhalation powder, hard capsules
Mannitol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmaxis

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Bronchitol 40 mg, inhalation powder, hard capsules Mannitol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bronchitol is and what it is used for
2. What you need to know before you use Bronchitol
3. How to use Bronchitol
4. Possible side effects
5. How to store Bronchitol
6. Contents of the pack and other information

1. What Bronchitol is and what it is used for

What Bronchitol is

Bronchitol contains a medicine called mannitol which is a mucolytic agent.

What Bronchitol is used for

Bronchitol is for use in adults 18 years of age and over. As well as using Bronchitol you will normally keep using the other medicines you take for cystic fibrosis.

How Bronchitol works

Bronchitol is inhaled into the lungs to help with cystic fibrosis, an inherited disease that affects the glands in the lungs, gut and pancreas that secrete fluids such as mucus and digestive juices.

Bronchitol helps by increasing the amount of water on the surface of your airways and in your mucus. This helps your lungs to clear mucus more easily. It also helps improve the condition of your lungs and your breathing. As a result you may get a 'productive cough', which also helps to remove mucus from your lungs.

2. What you need to know before you use Bronchitol

Do not use Bronchitol

- if you are allergic to mannitol
- if your doctor has not tested if you are sensitive to mannitol. Before you are started on Bronchitol, your doctor will check whether your airways are too sensitive to mannitol. If you are too sensitive to mannitol, your airways will become narrower, and you may find it harder to breathe.

If either of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using this medicine.

Warnings and precautions

- if you have asthma;

- if you have ever coughed up blood or had blood in your sputum;
- if you have severe cystic fibrosis, in particular if your lung function measured by the Forced Expiratory Volume in first second of expiration (FEV₁) is usually less than 30%.

Talk to your doctor or pharmacist before using this medicine.

Inhaling medicines can cause chest tightness and wheezing and this can happen immediately after taking this medicine. Your doctor will help you take your first dose of Bronchitol and check your lung function before, during and after dosing. Your doctor may ask you to use other medicines such as a bronchodilator before taking Bronchitol.

Inhaling medicines can also cause cough and this can happen with Bronchitol. Talk to your doctor if the cough won't go away or worries you.

Children and adolescents

Bronchitol must not be used by children and adolescents under the age of 18. This is because there is limited information in this group of people.

Other medicines and Bronchitol

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You can carry on using your medicines for cystic fibrosis when you are using Bronchitol, this includes inhaled antibiotics such as tobramycin and colistimethate sodium. If you are not sure, talk to your doctor or pharmacist before using Bronchitol.

Pregnancy and breast-feeding

- Talk to your doctor before using this medicine if you are pregnant, think you may be pregnant or are planning to become pregnant. You should avoid using this medicine if you are pregnant.
- Talk to your doctor before using this medicine if you are breast-feeding or plan to breast-feed. It is not known if this medicine passes into the breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines

Bronchitol is not likely to affect your ability to drive or use any tools or machines.

3. How to use Bronchitol

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Bronchitol is breathed in (inhaled) as a powder from the capsule using the inhaler supplied in the pack. Bronchitol capsules can only be used with the inhaler supplied in the pack.

Always take your bronchodilator before using Bronchitol.

The recommended dose is 400 mg (10 capsules) twice a day.

When to use this medicine

Use Bronchitol as part of your normal daily treatment routine. The suggested order is as follows, unless otherwise advised by your doctor:

1. Use your bronchodilator;
2. Wait 5 to 15 minutes;
3. Use your Bronchitol before physiotherapy if this is part of your treatment routine.

4. Dornase alfa (Pulmozyme) if this is part of your treatment routine
5. Inhaled antibiotics if this is part of your treatment routine

How much to use

Adults 18 years of age and over

Initiation dose

Before you are prescribed Bronchitol your doctor will help you take your first dose of Bronchitol and test your lung function at each step to make sure you aren't sensitive to mannitol. The first dose is taken in 4 steps:-

- Step 1 – 1 capsule (40 mg)
- Step 2 – 2 capsules (80 mg)
- Step 3 – 3 capsules (120 mg)
- Step 4 – 4 capsules (160 mg)

At the end of the initiation dose you will have taken 10 capsules (400 mg) which is the same as the usual dose.

Treatment dose (2-week packs)

- You must use Bronchitol every day.
- The usual dose is 10 capsules (400 mg) inhaled in the morning, and 10 capsules inhaled in the evening.
- Have the evening dose at least 2 to 3 hours before you go to bed.
- For the best results, inhale each capsule one after another, so there is as little delay as possible between capsules.

How to use your medicine

- **The capsules are for inhalation use only and should not be swallowed.**
- The powder in the capsules must only be inhaled using the inhaler included in the pack.
- Use a new inhaler each week.
- Each of the ten capsules is put into the inhaler one at a time.
- Inhale the contents of the capsule using the inhaler, with one or two breaths in.

For instructions on how to use the inhaler, see the end of the leaflet.

If you use more Bronchitol than you should

If you think you have used too much medicine, tell your doctor or pharmacist straight away. You may:

- feel that you cannot breathe;
- become wheezy;
- cough a lot.

The doctor may give you oxygen and medicines to help you breathe.

If you forget to use Bronchitol

- If you forget a dose, use it as soon as you remember it and carry on as usual. However, if it is nearly time for the next dose, skip the missed dose.
- Do not use a double dose to make up for a forgotten dose.

If you stop using Bronchitol

If you stop using Bronchitol your symptoms may get worse. Do not stop using your Bronchitol without talking to your doctor first, even if you feel better. Your doctor will tell you how long to use this medicine for.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Bronchitol and see a doctor straight away if you notice the following serious side effects:

- Difficulty breathing, which may be due to narrowing of the airways, worsening of asthma symptoms or wheezing. This happens commonly, which may affect up to 1 in 10 people.
- Coughing up blood or blood in your sputum. This happens commonly.

Tell your doctor straight away if you notice any of the following side effects:

- Severe cough. This happens commonly.
- Worsening of symptoms. This happens commonly.

Other side effects include:

Very common (may affect more than 1 in 10 people)

- Cough

Common

- Chest discomfort
- Headache
- Pain in the back of your mouth and throat and discomfort when swallowing
- Throat irritation
- Vomiting, vomiting after coughing

Uncommon (may affect up to 1 in 100 people)

- Burning or painful sensation on the tongue
- CF related diabetes
- Chest and abdominal pain
- Change in voice
- Cold sweat
- Congestion
- Dehydration
- Decreased appetite
- Diarrhoea
- Ear pain
- Feeling tired
- Feeling dizzy
- Feeling unwell
- Flu and fever
- Wind
- Heartburn
- Hernia pain
- Hyperventilation
- Itching, rash, acne
- Joint stiffness and pain
- Morbid thoughts
- Mouth ulcers
- Respiratory tract infection
- Runny nose
- Sputum infection
- Trouble sleeping
- Yeast infection of the mouth (thrush)
- Unintentional loss of urine

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V***. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bronchitol

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Store in the original package in order to protect from moisture.

Once removed from the blister strip a capsule should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bronchitol contains:

The active substance is mannitol. Each capsule contains 40 milligrams mannitol. Average inhaled dose per capsule is 32.2 milligrams mannitol.

What Bronchitol looks like and contents of the pack:

Bronchitol is a powder for inhalation that is filled into capsules. Bronchitol 40 mg inhalation powder, hard capsules contain a white or almost white powder filled into clear, colourless, hard, capsules with “PXS 40 mg” imprinted on them. The powder is inhaled into the lungs using the inhaler provided in the pack.

One initiation dose pack of Bronchitol contains 1 blister with 10 capsules and 1 inhaler. The initiation dose pack is used during the initiation dose assessment with your doctor.

One 2-week treatment pack of Bronchitol contains 28 blisters with 10 capsules each (280 capsules in total) and 2 inhalers. The 2-week treatment pack is for treatment use.

Marketing Authorisation Holder

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Manufacturer

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or

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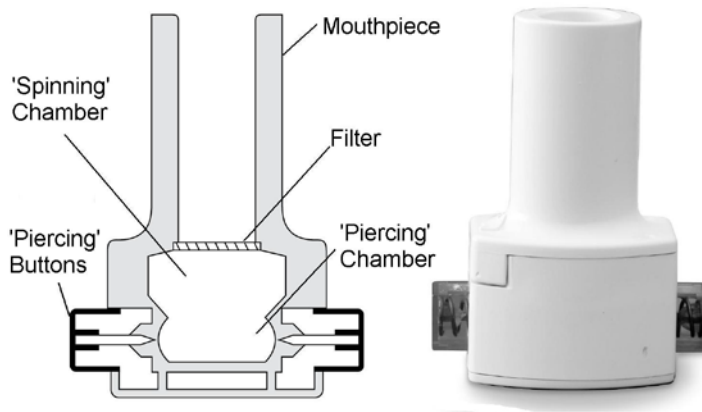
This leaflet was last revised in month YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu/>. There are also links to other websites about rare diseases and treatments.

How to use the inhaler

Below is a diagram that shows what the inhaler looks like. Bronchitol capsules can only be used with the inhaler provided in the pack.



Inhaler device

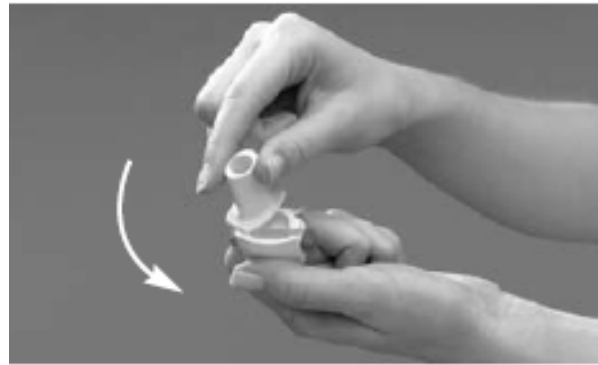
The following steps explain how to use the inhaler. For more advice on how to look after your inhaler, please see the end of the instructions.

- 1. Take off the cap**
 - Using both hands, hold the inhaler upright and take off the cap.



2. Open the inhaler

- Hold the bottom of the inhaler firmly with one hand.
- You should hold the inhaler along the bottom to make sure you don't press the piercing buttons.
- Then open it by turning the mouth-piece in the direction of the arrow on the inhaler.



3. Put in the capsule

- First make sure your hands are dry.
- Then take out a capsule from the blister (only remove the capsule just before use).
- Put the capsule into the capsule-shaped space in the bottom of the inhaler.



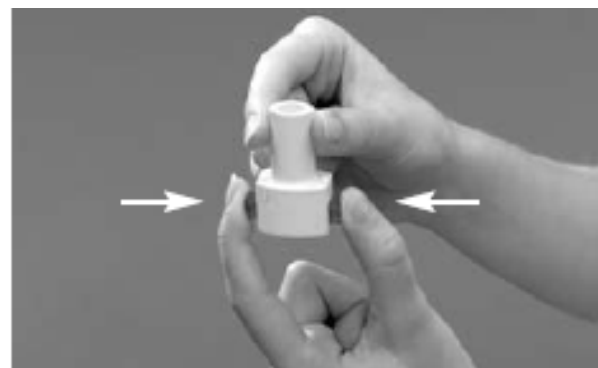
4. Close the inhaler

- Keep the inhaler in an upright position.
- Then twist the mouth-piece into the closed position - when it is closed you will hear a 'click'.



5. Make a hole in the capsule

- This lets the powder in the capsule be released when you breathe in. In this leaflet we call making the hole 'piercing'.
- Hold the inhaler upright and fully press in both 'Piercing' buttons on the sides of the inhaler at the same time, then release them. Only do this once. This is because piercing the capsule more than once may make it split or break-up.



6. Prepare for inhalation

- Tilt the inhaler so that the mouth-piece faces slightly downward.
- This allows the capsule to drop forward into the spinning chamber.
- Keep the inhaler tilted in this way and breathe out completely (away from the inhaler).



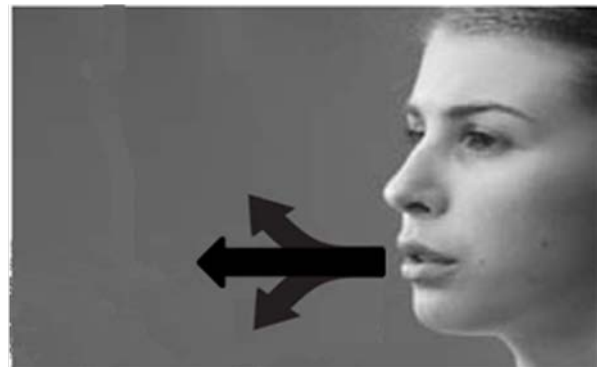
7. Inhale

- Tilt your head back slightly.
- Keeping the inhaler tilted downward, put the inhaler to your mouth and make sure you close your lips tightly around the mouth-piece.
- Take a steady deep breath in, to fill your lungs - then hold your breath for 5 seconds. When you breathe in you should hear a 'rattling' sound as the capsule spins in the inhaler. If this does not happen, the capsule may be stuck.
- If you do not hear the rattling, hold the inhaler with the mouth-piece facing downwards, and tap the bottom firmly. Do not try to loosen the capsule by pressing the piercing buttons again. Repeat the inhalation to get your dose.



8. Breathe out

- Take the inhaler away from your mouth.
- Breathe out, and then breathe normally again.



9. Check the capsule

- Look to see if the capsule is empty - the capsule must spin in the inhaler in order to empty. If the capsule has not emptied you may need to repeat steps 6 to 8.



10. Take out the used capsule

- Turn the inhaler upside down, tap the bottom and throw the empty capsule away.

11. Repeat steps 3 to 10 for each capsule

- Perform these steps for each of the ten capsules.
- To get the best results from Bronchitol, inhale each capsule one after another.

Extra information on how to look after your inhaler

- Keep your inhaler dry and always make sure your hands are dry before using it.
- Never breathe or cough into your inhaler.
- Never take your inhaler apart.
- Never place a capsule directly into the mouth-piece of your inhaler.
- Never leave a used capsule in your inhaler chamber.
- Use a new inhaler each week.
- If your inhaler breaks, use your second inhaler and talk to your doctor.

Cleaning the inhaler - Usually your inhaler will give you the correct dose of medicine for 7 days without needing cleaning. However, if your inhaler does need cleaning, the steps to follow are:

1. Ensure your inhaler is empty.
2. Wash your inhaler in warm water with the mouth-piece open.
3. Shake it until there are no large water droplets left in the inhaler.
4. Leave it to dry in the air - lay it on its side with the mouth-piece open.
5. You must let it fully dry, this can take up to 24 hours. While it is drying, use your other inhaler.