

**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**

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's initiation dose of Bronchitol 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 (SpO<sub>2</sub>), and manage acute bronchospasm (see sections 4.4 and 4.8) 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<sub>1</sub> and SpO<sub>2</sub> (Oxygen saturation in the blood) measurement. All FEV<sub>1</sub> measurements and SpO<sub>2</sub> 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 FEV<sub>1</sub> and SpO<sub>2</sub> is measured prior to the initiation dose
- Step 2: Patient inhales 40 mg (1x40 mg capsules) and SpO<sub>2</sub> is monitored
- Step 3: Patient inhales 80 mg (2x40 mg capsules) and SpO<sub>2</sub> is monitored
- Step 4: Patient inhales 120 mg (3x40 mg capsules), FEV<sub>1</sub> is measured and SpO<sub>2</sub> is monitored
- Step 5: Patient inhales 160 mg (4x40 mg capsules), FEV<sub>1</sub> is measured and SpO<sub>2</sub> is monitored
- Step 6: Patients FEV<sub>1</sub> 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 FEV<sub>1</sub> 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.

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.

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

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)

#### Special populations

##### *Elderly patients (≥65 years)*

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

##### *Renal or hepatic impairment*

Bronchitol has not formally 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.

##### *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 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 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, it must be ensured that the device is empty, then it should be washed in warm water and before re-use, the inhaler should be allowed 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<sub>2</sub> at any point of the assessment;
- FEV<sub>1</sub> fall from baseline is  $\geq 20\%$  at 240 mg cumulative dose;
- FEV<sub>1</sub> has fallen 20- $<50\%$  (from baseline) at the end of the assessment and does not return to  $<20\%$  within 15 minutes;
- FEV<sub>1</sub> has fallen  $\geq 50\%$  (from baseline) at the end of the assessment.

If a therapy induced hyperresponsive reaction is suspected, Bronchitol should be discontinued. All patients should be monitored until their FEV<sub>1</sub> has returned to baseline levels.

#### 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 active substance induced bronchospasm. The initiation dose assessment described in section 4.2 should be repeated if uncertainty exists.

#### Asthma

The safety/efficacy 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 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  $\geq 240$  ml in a 24-hour period
- recurrent bleeding  $\geq 100$  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 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 FEV<sub>1</sub> 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.

There are no data on concomitant use of hypertonic saline with Bronchitol as it was excluded from the Phase 3 studies.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are limited data 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

The safety profile of Bronchitol has been evaluated in clinical studies involving more than 1200 patients. (See Table 1).

### Initiation dose assessment

The most commonly observed adverse reaction associated with the use of Bronchitol during the initiation dose assessment is cough (2.9% 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 8.3% of patients compared to 4.0% of patients in the control arm. Cough which led to cessation of treatment was also commonly experienced and was observed in 4.0% 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%, 3.3% and 3.4% in the Bronchitol arms for studies 301, 302 and 303 respectively vs. 3.4%, 0% and 5.6% in the control arms. The proportion of patients who experienced haemoptysis including haemoptysis reported during exacerbation was 7.0% in the mannitol arm and 7.7% in the control arm (see section 4.4).

### Tabulated list of adverse reactions

The safety profile of Bronchitol is based on the safety data from Phase III clinical studies (including data from the initiation dose assessment).

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 in the phase 3 studies (initiation dose assessment and/or treatment phase)

<u>System organ class</u>	<u>Frequency</u>	<u>Adverse Reaction</u>
Infections and infestations	Uncommon	Bacterial disease carrier, Bronchitis, Bronchopneumonia, Lung infection, Oral candidiasis, Pharyngitis, Staphylococcal infection, Upper respiratory tract infection
Metabolism and nutrition disorders	Uncommon	Decreased appetite, CF related diabetes, Dehydration
Psychiatric disorders	Uncommon	Initial insomnia, Morbid thoughts
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
Ear and labyrinth disorders	Uncommon	Ear pain
Respiratory, thoracic and mediastinal disorders	Common	Cough, Haemoptysis, Oropharyngeal pain, Wheezing
	Uncommon	Productive cough, Throat irritation, Asthma, Bronchospasm, Forced expiratory volume decreased, Rhinorrhoea, Dyspnoea, Dysphonia, Hyperventilation, Obstructive airways disorder, Respiratory tract congestion, Sputum discoloured, Hypoxia
Gastrointestinal disorders	Common	Post-tussive vomiting, Vomiting
	Uncommon	Nausea, Diarrhoea, Eructation, Flatulence, Gastroesophageal reflux disease, Glossodynia, Retching, Stomatitis, Abdominal pain upper, Aphthous Stomatitis, Odynophagia

Skin and subcutaneous tissue disorders	Uncommon	Acne, Cold sweat, Pruritus, Rash, Rash pruritic
Musculoskeletal and connective tissue disorders	Uncommon	Musculoskeletal chest pain, Arthralgia, Back pain, Joint stiffness, Musculoskeletal pain
Renal and urinary disorders	Uncommon	Urinary incontinence
General disorders and administration site conditions	Common	Condition aggravated, Chest discomfort
	Uncommon	Pyrexia, Fatigue, Influenza like illness, Hernia pain, Malaise, Chest pain
Investigations	Uncommon	Blood alkaline phosphatase increased, Bacteria or fungus sputum test positive

Adverse reactions that occurred-only with-the-initiation dose assessment (MTT) are dehydration, forced expiratory volume decreased, hypoxia, diarrhoea, abdominal pain upper, aphthous stomatitis, odynophagia, chest pain and blood alkaline phosphatase increased.

#### Description of selected adverse reactions

Twenty seven (7.1%) out of 378 patients who undertook the mannitol tolerance test (MTT) in study 301, 18 (5.3%) out of 341 patients in study 302 and 25 (5.1%) out of 486 patients in Study 303 had a positive (MTT). In study 301, overall the most frequently reported adverse reactions during the MTT were cough in 20 (5.3%) subjects, wheezing/bronchospasm in seven (1.9%) subjects and chest discomfort in six (1.6%) subjects. In study 302 the most frequent adverse reaction reported during the MTT was cough in seven patients (2.1%), and in study 303 the most frequently reported adverse reaction from the MTT was also cough in eight patients (1.6%).

#### 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 (6 to 17 years of age)*

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(6 to 17 years of age)*

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 in the phase 3 studies (initiation dose assessment and/or treatment phase) – paediatric population (6 to 17 years of age)

System organ class	Frequency	Adverse Reaction
Psychiatric disorders	Uncommon	Initial insomnia
Nervous system	Common	Headache
	Uncommon	Dizziness
Ear and labyrinth disorders	Uncommon	Ear Pain
Respiratory, thoracic and mediastinal disorders	Common	Cough, Condition aggravated, Haemoptysis, Oropharyngeal pain, Chest discomfort, Wheezing, Asthma, Productive cough
	Uncommon	Bronchitis, Bronchopneumonia, Dysphonia, Hyperventilation, Sputum Discoloured, Throat irritation, Pharyngitis, Upper respiratory tract infection, Bronchospasm, Dyspnoea,-Chest pain
Gastrointestinal disorders	Common	Vomiting, Post-tussive vomiting
	Uncommon	Nausea, Odynophagia, Retching
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, Pruritic rash

Musculoskeletal and connective tissue disorders	Uncommon	Musculoskeletal chest pain
Renal and urinary disorders	Uncommon	Urinary incontinence
General disorders and administration site conditions	Uncommon	Pyrexia
Investigations	Common	Bacteria sputum identified

Adverse reactions that occurred only with-initiation dose assessment (MTT) are bronchospasm, chest pain, odynophagia and retching

#### 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 beta<sub>2</sub> 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 FEV<sub>1</sub> 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

Three Phase 3, 26-week double blind, randomised, parallel arm, controlled, intervention studies (DPM-CF-301, DPM-CF-302 and DPM-CF-303) 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). 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. Twenty seven (7.1%) out of 378 patients who undertook the mannitol tolerance test (MTT) in study 301, 18 (5.3) out of 341 patients in study 302 and 25 out of 486 patients (5.1%) in study 303 had a positive MTT defined as either 1) a fall in FEV<sub>1</sub> >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 FEV<sub>1</sub> > 50% from baseline at end of test (step 6) or 4) who had a fall in SpO<sub>2</sub> to < 89% during the procedure. An additional 2.8% (n=34) of patients from the three studies had incomplete MTTs and were not randomised.

Mean (SD) baseline FEV<sub>1</sub> 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-303 (N=423) the baseline FEV<sub>1</sub> percent predicted was 63.17 (SD: 15.15) and 62.98 (SD: 13.65). In study DPM-CF-301 64.4 % of the patient population were adults while in study



DPM-CF-302 this figure was 49.5%. Study DPM-CF-303 was all adult patients. Fifty five % of patients were receiving rhDNase in study DPM-CF-301 while in study DPM-CF-302 this number was 75% and for DPM-CF-303 this was 67.6%. The percentage of patients receiving inhaled antibiotics was 55% in study DPM-CF-301, 56% in study DPM-CF-302 and 52% in Study DPM-CF-303. Concomitant administration with hypertonic saline was not permitted in these trials.

The primary pre-specified endpoint i.e. the change from baseline in FEV<sub>1</sub> (ml) in the modified ITT (mITT) population (n=269, 297 and 423 in studies DPM-CF-301, DPM-CF-302 and DPM-CF-303, respectively) compared to control over the 26 weeks period is provided in Table 3 alongside FEV<sub>1</sub> presented as absolute and relative change % predicted.

Table 3 – Change in FEV<sub>1</sub> from baseline over 26 weeks in the mITT and adult populations

	Effect size estimate					
	DPM-CF-301		DPM-CF-302		DPM-CF-303	
	FEV <sub>1</sub> (95% CI)	p value	FEV <sub>1</sub> (95% CI)	p value	FEV <sub>1</sub> (95% CI)	p value
	Overall Population					
	N=269		N=297		N=423	
<b>Absolute mL</b>	<b>94.5</b> (46.2, 142.7)	<b>&lt;0.001</b>	<b>54.1</b> (-1.97, 110.3)	<b>0.059</b>	<b>54</b> (8, 100)	<b>0.020</b>
<b>Absolute % predicted</b>	<b>2.4</b> (0.9, 3.9)	<b>0.001</b>	<b>1.9</b> (-0.02, 3.8)	<b>0.052</b>	<b>1.2</b> (0.07, 2.4)	<b>0.037</b>
<b>Relative % predicted</b>	<b>3.5</b> (1.0, 6.1)	<b>0.007</b>	<b>3.6</b> (0.3, 6.9)	<b>0.033</b>	<b>2.3</b> (0.3, 4.2)	<b>0.024</b>
	Adult Population					
	N=171		N=144		N=423	
<b>Absolute mL</b>	<b>108.5</b> (47.6, 169.4)	<b>&lt;0.001</b>	<b>85.9</b> (4.6, 167.3)	<b>0.038</b>	<b>54</b> (8, 100)	<b>0.020</b>
<b>Absolute % predicted</b>	<b>2.7</b> (0.9, 4.5)	<b>0.004</b>	<b>2.3</b> (-0.4, 5.1)	<b>0.095</b>	<b>1.2</b> (0.07, 2.4)	<b>0.037</b>
<b>Relative % predicted</b>	<b>4.3</b> (1.1, 7.5)	<b>0.008</b>	<b>5.0</b> (0.2, 9.8)	<b>0.040</b>	<b>2.3</b> (0.3, 4.2)	<b>0.024</b>

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 (BOCF) approach whereas no imputation was performed in DPM-CF-301 or DPM-CF-302.

The treatment effect of Bronchitol on FEV<sub>1</sub> was less evident in the subgroup of patients who were receiving concomitant rhDNase. In rhDNase users in study 301 the relative change in FEV<sub>1</sub> % 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. In study 303 the relative change (95% CI) for rhDNase users and non-users was 1.30 (-0.91, 3.51) and 4.45 (0.52, 8.38), respectively.

Study 303 did not show a superior treatment effect of Bronchitol on FEV<sub>1</sub> for female patients, in whom the underlying cystic fibrosis disease course may be worse than males for reasons that are not fully understood. In female patients, the adjusted mean change in FEV<sub>1</sub> was 27ml for Bronchitol and 44ml for the control arm, suggesting potentially inferior benefit on lung function with Bronchitol compared to the control, although the difference was not statistically significant (p=0.480).

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. In study 303 13.4% subjects in the mannitol arm and 13.6% 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 and 40 ml (95% CI: -12, 92) in study 303.

#### Paediatric population

The safety and efficacy of Bronchitol in children and adolescents aged less than 18 years has not been established (see section 4.2).

In studies DPM-CF-301 and 302 relative % predicted FEV<sub>1</sub> 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 FEV<sub>1</sub> 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<sub>max</sub> 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.

The limited data available in adolescents aged 12 to 17 years 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.

Store in the original blister in order to protect from moisture. The capsules must only be removed immediately before use.

#### **6.5 Nature and contents of container**

Aluminium/polyamide/PVC/aluminium blisters. Cartons containing 10 or 280 capsules for initial dose and treatment use respectively.

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

The 2-week carton contains 28 blisters (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 Europe Limited  
108 Q House,  
Furze Road,  
Sandyford,  
Dublin 18,  
D18AY29  
Ireland

### **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 April 2012

Date of latest renewal: 11 January 2017

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

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

MIAS Pharma Limited  
Suite 1, Stafford House  
Strand Road, Portmarnock  
Co. Dublin, D13WC83  
Ireland

Or

Arvato Supply Chain Solutions SE  
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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

### **• Additional risk minimisation measures**

Prior to launch of the medicinal 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.

**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  
Store in the original blister in order to protect from moisture.

**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 Europe Limited  
108 Q House,  
Furze Road,  
Sandyford,  
Dublin 18,  
D18AY29  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/760/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Bronchitol 40 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**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  
Store in the original blister in order to protect from moisture.

**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 Europe Limited  
108 Q House,  
Furze Road,  
Sandyford,  
Dublin 18,  
D18AY29,  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/12/760/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Bronchitol 40 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN

**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 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**

Talk to your doctor or pharmacist before using this medicine:

- 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 (FEV<sub>1</sub>) is usually less than 30%.

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 should 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**

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should avoid using this medicine if you are pregnant.
- If you are breast-feeding or plan to breast-feed ask your doctor for advice before using this medicine. It is not known if this medicine passes into the breast milk.

### **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.

Always take your bronchodilator before using Bronchitol.

### **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.

#### Order of using 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 to use your medicine

- Bronchitol is breathed in (inhaled) as a powder from the capsule using the inhaler supplied in the pack. It is for inhalation use only and must not be administered by any other route. The capsules must 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:**

Common (May affect up to 1 in 10 people)

- Cough
- Chest discomfort
- Headache
- Pain in the back of your mouth and throat and discomfort when swallowing
- 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 sick (nausea)
- 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
- Throat irritation
- 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 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 hard 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**

Pharmaxis Europe Limited, 108 Q House, Furze Road, Sandyford, Dublin 18, D18AY29, Ireland.

### **Manufacturer**

MIAS Pharma Limited, Suite 1, Stafford House, Strand Road, Portmarnock, Co. Dublin, D13WC83, Ireland or Arvato Supply Chain Solutions SE, Gottlieb-Daimler Straße 1, 33428 Harsewinkel, North Rhine-Westphalia Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

Pharmaxis Europe Limited  
Tél/Tel: + 353 (0) 1431 9816

#### **Lietuva**

Pharmaxis Europe Limited  
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#### **България**

Pharmaxis Europe Limited  
Тел.: + 353 (0) 1431 9816

#### **Luxembourg/Luxemburg**

Pharmaxis Europe Limited  
Tél/Tel: + 353 (0) 1431 9816

#### **Česká republika**

4 Life Pharma CZ, s.r.o.  
Tel: +420 244 403 003

#### **Magyarország**

Pharmaxis Europe Limited  
Tel.: + 353 (0) 1431 9816

**Danmark**

Chiesi Pharma AB  
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**Deutschland**

Chiesi GmbH  
Tel: +49 (0) 40 897 240

**Eesti**

Pharmaxis Europe Limited  
Tél/Tel: + 353 (0) 1431 9816

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Chiesi Farmaceutici S.p.A.  
Tel: + 39 0521 2791

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Pharmaxis Europe Limited  
Sími: + 353 (0) 1431 9816

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Chiesi Italia S.p.A.  
Tel: +39 0521 2791

**Κύπρος**

Chiesi Hellas A.E.B.E.  
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**Nederland**

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**Norge**

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Tlf: + 46 8 753 35 20

**Österreich**

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Pharmaxis Europe Limited  
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**Slovenská republika**

4 Life Pharma SK, s.r.o.  
Tel: + 420 244 403 003

**Suomi/Finland**

Chiesi Pharma AB  
Puh/Tel: + 46 8 753 35 20

**Sverige**

Chiesi Pharma AB  
Tel: + 46 8 753 35 20

**United Kingdom (Northern Ireland)**

Chiesi Farmaceutici S.p.A.  
Tel: + 39 0521 2791

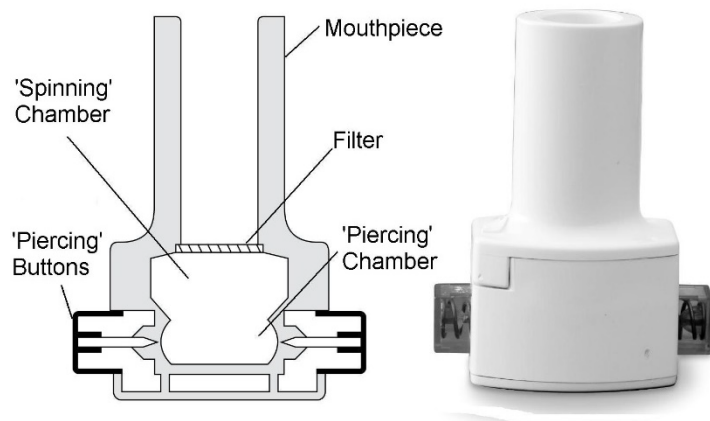
**This leaflet was last revised in MM/YYYY.**

**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.



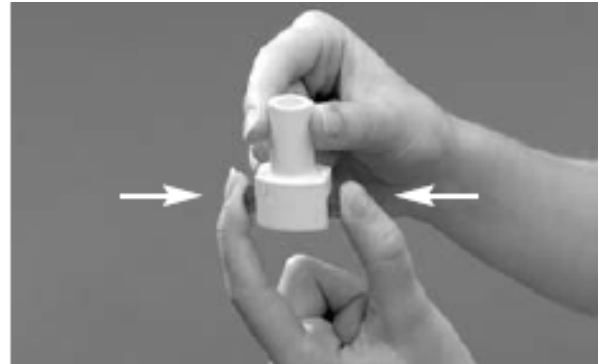
**4. Close the inhaler**

- 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**

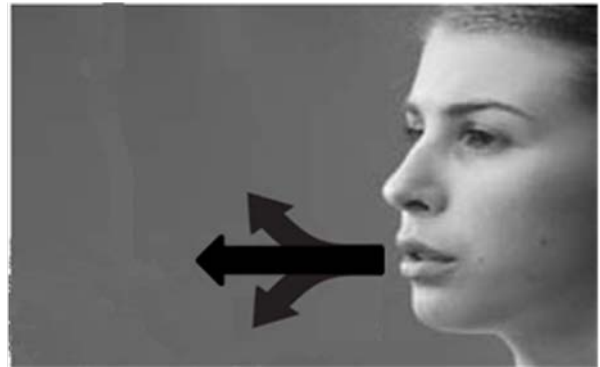
- Tilt your head back slightly.
- Keeping the inhaler tilted downward, put the inhaler to your mouth and make sure you close your lips tightly around the mouth-piece.
- Take a steady deep breath in, to fill your lungs - then hold your breath for 5 seconds. When you breathe in you should hear a 'rattling' 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.