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_2), 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_1 and SpO_2 (Oxygen saturation in the blood) measurement. All FEV_1 measurements and SpO_2 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_1 and SpO_2 is measured prior to the initiation dose
Step 2: Patient inhales 40 mg (1x40 mg capsules) and SpO_2 is monitored
Step 3: Patient inhales 80 mg (2x40 mg capsules) and SpO_2 is monitored
Step 4: Patient inhales 120 mg (3x40 mg capsules), FEV_1 is measured and SpO_2 is monitored
Step 5: Patient inhales 160 mg (4x40 mg capsules), FEV_1 is measured and SpO_2 is monitored
Step 6: Patients FEV_1 is measured 15 minutes post initiation dose.

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_1 has returned to baseline levels.

Therapeutic dose regimen
The therapeutic dose regimen should not be prescribed until the initiation dose assessment has been performed. The patient must complete and pass the initiation dose assessment before starting treatment with Bronchitol.

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)

<u>Special populations</u>

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:

- ≥10% fall from baseline in SpO_2 at any point of the assessment;
- FEV_1 fall from baseline is ≥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 ≥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_1 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 ≥240 ml in a 24-hour period
- recurrent bleeding ≥100 ml/day over several days

The reinstitution or withholding of Bronchitol following smaller episodes of haemoptysis should be based on clinical 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_1 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≥1/100,000 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)

System organ class	Frequency	Adverse Reaction
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, Gastrooesophageal 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 patientsin 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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Susceptible persons may suffer bronchoconstriction in the event of an inhaled overdose. If excessive coughing and bronchoconstriction occurs, a beta$_2$ 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_1 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_1 >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_1 > 50% from baseline at end of test (step 6) or 4) who had a fall in Sp02 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_1 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_1 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_1 (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_1 presented as absolute and relative change % predicted.

Table 3 – Change in FEV_1 from baseline over 26 weeks in the mITT and adult populations

	Effect size estimate					
	DPM-CF-301		**DPM-CF-302**		**DPM-CF-303**	
	FEV_1 (95% CI)	**p value**	**FEV_1 (95% CI)**	**p value**	**FEV_1 (95% CI)**	**p value**
	Overall Population					
	N=269		**N=297**		**N=423**	
Absolute mL	**94.5** (46.2, 142.7)	**<0.001**	**54.1** (-1.97, 110.3)	**0.059**	**54** (8, 100)	**0.020**
Absolute % predicted	**2.4** (0.9, 3.9)	**0.001**	**1.9** (-0.02, 3.8)	**0.052**	**1.2** (0.07, 2.4)	**0.037**
Relative % predicted	**3.5** (1.0, 6.1)	**0.007**	**3.6** (0.3, 6.9)	**0.033**	**2.3** (0.3, 4.2)	**0.024**
	Adult Population					
	N=171		**N=144**		**N=423**	
Absolute mL	**108.5** (47.6, 169.4)	**<0.001**	**85.9** (4.6, 167.3)	**0.038**	**54** (8, 100)	**0.020**
Absolute % predicted	**2.7** (0.9, 4.5)	**0.004**	**2.3** (-0.4, 5.1)	**0.095**	**1.2** (0.07, 2.4)	**0.037**
Relative % predicted	**4.3** (1.1, 7.5)	**0.008**	**5.0** (0.2, 9.8)	**0.040**	**2.3** (0.3, 4.2)	**0.024**

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_1 was less evident in the subgroup of patients who were receiving concomitant rhDNase.In rhDNase users in study 301 the relative change in FEV_1 % 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_1 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_1 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_1 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_1 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.

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 (≤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

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