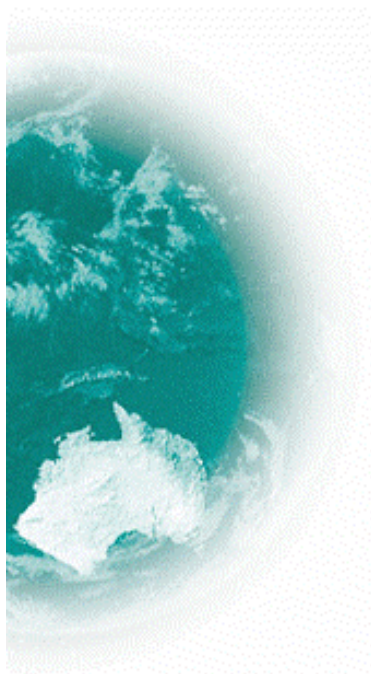




Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Mannitol

Proprietary Product Name: Bronchitol
Submission No: PM-2009-03748-3-5
Sponsor: Pharmaxis Ltd



March 2011

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	7 February 2011
<i>Active ingredient(s):</i>	Mannitol
<i>Product Name(s):</i>	Bronchitol
<i>Sponsor's Name and Address:</i>	Pharmaxis Ltd Locked Bag 5015 Frenchs Forest NSW 2086
<i>Dose form(s):</i>	Powder for inhalation in hard capsules
<i>Strength(s):</i>	40 mg
<i>Container(s):</i>	Foil blister pack
<i>Pack size(s):</i>	10 capsules with one inhaler 140 capsules with one inhaler 280 capsules with two inhalers
<i>Approved Therapeutic use:</i>	Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above as either an add-on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to dornase alfa.
<i>Route(s) of administration:</i>	Inhalation
<i>Dosage:</i>	The recommended dose is 400mg twice daily by inhalation, that is, 10 capsules twice daily given 15 minutes after a bronchodilator.
<i>ARTG Number:</i>	168002

Product Background

This AusPAR describes the evaluation of a submission by Pharmaxis Ltd to register Bronchitol containing 40 mg mannitol powder for inhalation for use in the treatment cystic fibrosis. The recommended dose is 400 mg (ten capsules) twice a day. The proposed Bronchitol 40 mg capsules are very similar to the registered Aridol 40 mg capsules.

Bronchitol (mannitol) is an inhaled hyperosmotic agent that is stated to be deposited in the respiratory tract, resulting in increased water in the in the airway lumen, and increased hydration of respiratory mucous secretions. This is proposed to lead to improved clearance of mucous. Cystic fibrosis is a condition where there are thick, tenacious respiratory secretions that are difficult to clear, leading to airway obstruction and chronic infections.

The currently approved indication in Australia is:

Identifying bronchial hyperresponsiveness to assist in the diagnosis of asthma.

The proposed indication in Australia is:

Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above as either add-on therapy to rhDNase or in patients intolerant to or inadequately responsive to rhDNase¹.

Inhaled dry powder mannitol, Aridol, was approved in Australia in March 2006 for *identifying bronchial hyperresponsiveness*. Aridol (an otherwise very similar product) is presented in strengths of 5 mg, 10 mg, 20 mg and 40 mg.

The 244th meeting of the Australian Drug Evaluation Committee (ADEC) (which preceded the Advisory Committee on Prescription Medicines [ACPM]) considered an application by Pharmaxis to register Aridol in February 2006 for “*identifying bronchial hyperresponsiveness to assist in the diagnosis (and management) of diseases of the airways associated with inflammation (eg asthma, exercise induced asthma, chronic obstructive pulmonary disease with a component of asthma)*”. The proposed dosage regimen was: administration of sequential doses of 5, 10, 20, 40, 80, 160, 160 and 160 mg (maximum cumulative dose = 635 mg), with the patient’s forced expiratory volume in one second (FEV₁) being measured after each dose. The test is terminated if the patient’s FEV₁ decreases by 15% or more from baseline (positive response), or if the cumulative dose of 635 mg is reached. The Delegate noted that the pivotal study only examined the efficacy and safety of the product in the context of diagnosing asthma. While a small Phase II study suggested that Aridol may have a role in the “management of diseases of the airways associated with inflammation”, the experience in this context was very limited and more extensive data was required before such an indication could be approved.

The ADEC noted that the evidence for efficacy was primarily derived from the single large randomised controlled trial. The primary efficacy endpoints were the sensitivity and specificity of the mannitol challenge compared to the hypertonic saline challenge using a cut-off of a 15% fall in FEV₁ for determining a positive result. The two tests produced comparable mean reductions in FEV₁. The Committee considered that a more informative endpoint was the performance of the mannitol challenge against the clinical diagnosis of asthma. The mannitol challenge had a sensitivity of only 59.8% but had a high specificity of 95.2%. These results were comparable to those achieved with the hypertonic saline challenge (sensitivity = 65.1 %; specificity = 95.2%). The mannitol challenge test will have a low rate of false positives and therefore should be useful in confirming the diagnosis of asthma. The test will, however, have a fairly high rate of false negatives, as about 40% of clinically diagnosed asthmatics will have a negative test. The currently available data were insufficient to support an indication for monitoring the control of asthma.

The Committee recommended approval of the product for “*identifying bronchial hyper-responsiveness to assist in the diagnosis of asthma*”, based on the submitted data.

An application was made in 2008 to register Bronchitol (same presentation as now proposed) for the following indication, “*Bronchitol is indicated for the treatment of patients with bronchiectasis to relieve symptoms affecting quality of life*”. The application was withdrawn, after the receipt of the overview, for commercial reasons.

Regulatory Status

Aridol capsules containing 5, 10, 20 and 40 mg of mannitol powder for inhalation were registered by Pharmaxis in 2006 for use in identifying bronchial hyper-responsiveness.

Bronchitol was designated as an Orphan Drug in Australia on 16 April 2009 for the treatment of patients with cystic fibrosis to improve lung function and reduce pulmonary exacerbations.

¹ “rhDNase” is an unacceptable synonym for dornase alfa (Pulmozyme) which is registered in Australia for the management of demonstrated respiratory complications in cystic fibrosis.

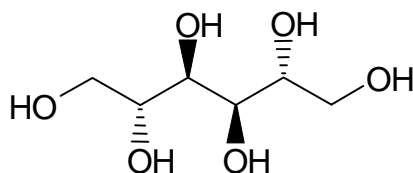
An application similar to the current Australian application has been submitted to the European Union (EU) in October 2009 via the Centralised Procedure.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)



mannitol

C₆H₁₄O₆ MW 182.2 CAS No. 69-65-8

Mannitol is a naturally occurring, enantiomerically pure, sugar alcohol. It is an isomer of sorbitol. Mannitol occurs as white, odourless, non-hygroscopic crystalline powder. It has a sweet taste. It is freely soluble in water.

Mannitol is quite widely used as a pharmaceutical excipient in oral and injection products registered in Australia, for example, mannitol 10% (w/v) 1000 mL and 20% (w/v) 500 mL intravenous infusion bags. There are European, British and United States pharmacopoeial monographs for mannitol and for mannitol infusions. The mannitol contains about 1% sorbitol; levels of other impurities are low. Control of mannitol is considered acceptable.

Drug Product

The proposed Bronchitol inhalation capsules are hard gelatin capsules containing only very fine mannitol. The capsules are filled with 40 mg of very fine mannitol powder which is prepared by spray drying. The capsule shells are not intended to be inhaled. The capsules are presented in blister foils, presented in a carton containing either 10 capsules with one inhaler device, or 280 capsules with two inhalers.

In use some of the mannitol is left in the capsule or deposits in the inhaler device. *In vitro* testing suggests that the total delivered dose (equivalent to the total into the patient's mouth) should be about 32 mg. The 'fine particle dose', an *in vitro* estimate of the amount delivered to the lung, is controlled by aerodynamic particle size distribution testing. The pivotal clinical trial in cystic fibrosis sufferers was Study DPM-CF-301. This study used seven batches of Bronchitol, and the limits proposed for fine particle dose match that measured for these batches.

New inhalation products are now normally labelled with the dose which is **delivered** from the inhaler device to the patient. For capsule products, however, labelling with the total amount in the capsule is the formal TGA requirement. The Aridol products were developed to contain integer amounts of mannitol per capsule. Both products are labelled with this amount. The evaluator requested that the sponsor should also include indicative delivered doses in the Product Information.

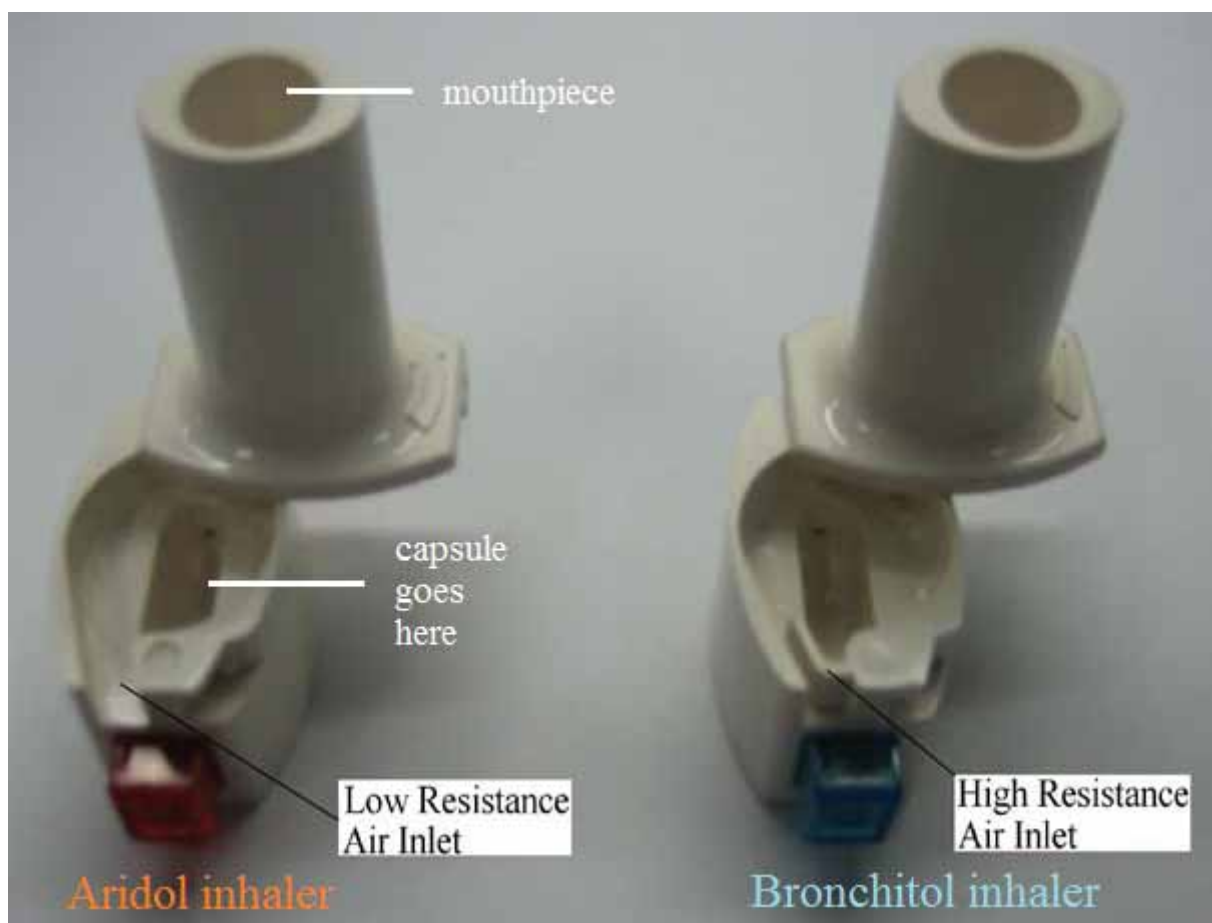
In vitro data indicate that Bronchitol may occasionally deliver individually high doses. The sponsor attributes this to mannitol accumulating in the device and notes that the total dose from 10 capsules is not affected.

Inhaler

The capsules are presented in packs with one or two inhaler devices. The device is used with one capsule at a time. It opens so that a capsule can be inserted in a cavity. Pushing two buttons punctures the capsule with stainless steel needles. The buttons are released and then inhalation through the mouthpiece spins the pierced capsule, releasing the mannitol powder. The mouthpiece tube incorporates a coarse sieve (not visible in Figure 1) which prevents inhalation of large capsule shell fragments (although the capsules do not appear to shatter significantly in use).

The inhaler to be supplied with Bronchitol is closely related to, but not the same, as that supplied with Aridol. Aridol is supplied with the low resistance (LR) model fitted with red buttons. Bronchitol will be supplied with the high resistance (HR) model fitted with blue buttons. The devices only differ functionally in the air inlet dimensions (Figure 1).

Figure 1: Photographs of the Aridol and Bronchitol inhalers



The sponsor chose the high resistance inhaler for this indication because in the early clinical trial DPM-CF-201 the first two adult patients experienced marked cough using a lower resistance inhaler. The change in inhaler apparently reduced the incidence of cough. The high resistance inhaler was used subsequently in cystic fibrosis studies.

The delivered dose and lung doses from a dry powder inhaler are affected by a patient's inspiratory profile (including volume) and the inhaler resistance. The sponsor has determined the inspiratory flow patterns of cystic fibrosis patients (and patients with other diseases). *In vitro* data show the expected dependence with higher mannitol delivery with higher inspired volume and faster

inspiratory flow. *In vitro* study of the fine particle dose used fixed flow rates only (28, 60 and 90 L/min) with 2 L and 4 L volumes. The fine particle doses at 28 and 60 L/min were quite similar.

The sponsor concluded that patients with baseline FEV₁ < 1 L may not be able to achieve the satisfactory inspiratory flow. Repeat inhalations with each capsule can be used to increase lung delivery.

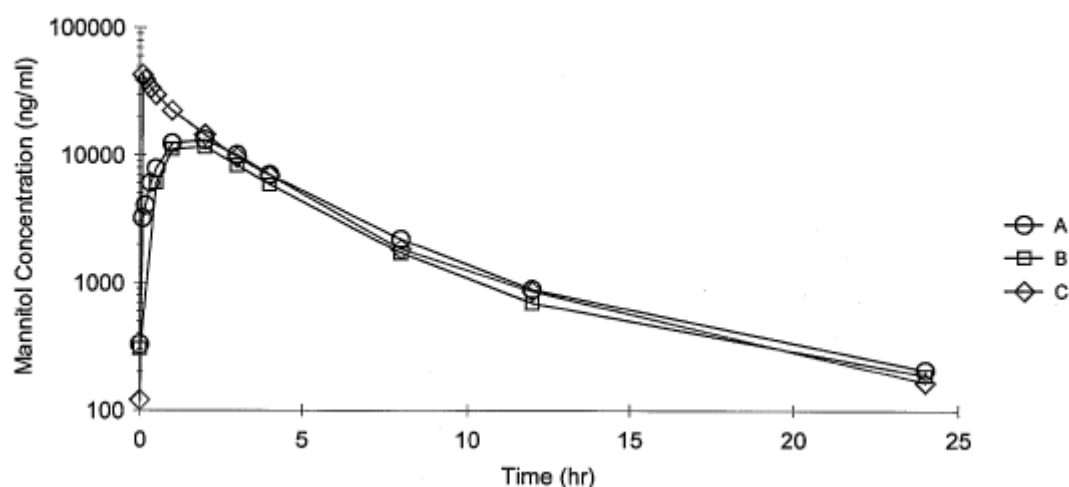
Bioavailability

Bronchitol is intended for local action in the lung and bioavailability data provide limited information on product exposure.

The sponsor submitted a pharmacokinetics study (DPM-PK-101) which provides a pharmacokinetic comparison of inhaled, oral solution and intravenous doses of mannitol. This was a randomised, open, three-way crossover study in 18 healthy adult volunteers. The mannitol doses were '635 mg' inhaled as Aridol capsules; 500 mg in 50 mL water orally (solution); and 500 mg as a 10% intravenous solution. The study used the low resistance inhaler provided with Aridol; the 635 mg dose is the maximum recommended Aridol dose (1 x 5 mg + 10 mg + 20 mg + 15 x 40 mg capsules) inhaled sequentially as quickly as practicable. The total of 635 mg is the capsule contents, not the delivered dose, which is probably about 540 mg. There was a 7 day washout between doses.

Plasma and urine samples were analysed for mannitol. The profiles following oral and inhaled doses were similar. Mean plasma profiles are shown in Figure 2.

Figure 2: Mean mannitol concentrations: A-inhalation (635 mg); B-oral (500 mg); C-intravenous (500 mg)



A-Inhalation (635 mg); B-Oral (500 mg); C-Intravenous (500 mg)

The mean absolute bioavailability of the inhaled mannitol was 59% (standard deviation [SD] 15). This was similar to the absolute bioavailability of oral mannitol: 63% (SD 14). Mean urinary excretion over 24 hours was about 55% for the inhalation and oral doses and 87% for the intravenous dose. Thus systemic exposure following Bronchitol inhalation is similar to that of an oral solution (based on delivered dose). The sponsor attributes this to significant mucociliary clearance of the lung dose.

Quality Summary and Conclusions

Given the close similarity of Aridol and Bronchitol, this application was not referred to the Pharmaceutical Subcommittee of the ACPM.

Registration was recommended with respect to chemistry and quality control aspects.

III. Nonclinical Findings

Introduction

The submission contained a small amount of new data. This report is chiefly based on data submitted and evaluated in the sponsor's previous applications.

Pharmacology

Mannitol is a hyperosmotic agent. Of relevance to the proposed new indication (treatment of cystic fibrosis), induction of mucin secretion in the ferret trachea *in vitro* (Kishioka *et al.*, 2003), and increased respiratory tract fluid output in the trachea of beagle dogs (Chen and Yeates, 2001) and cats (Peatfield *et al.*, 1986) *in vivo* have been shown with mannitol in previously evaluated studies published in the literature.^{2,3,4}

Safety pharmacology

No specialised safety pharmacology studies have been conducted with inhaled mannitol. However, effects on cardiovascular and respiratory function were monitored in the 2- and 26-week general repeat-dose inhalational toxicity studies in dogs previously submitted, with no effects on heart rate, electrocardiogram (ECG), respiratory rate, tidal volume or minute volume observed. Based on body surface area, the maximum dose tested in these studies (834 mg/kg/day) is 32- and 17-times higher than the maximum recommended human dose (800 mg/day) in an adult (50 kg) and children (6 years old), respectively.

Mannitol is not considered to be neurotoxic. No notable effects on the central nervous system (CNS) were observed in repeat-dose toxicity studies in rats and dogs following inhalation of the drug at doses up to 1124 mg/kg/day and 834 mg/kg/day in the respective species. Adjusted for body surface area, these doses are 13- and 32-times higher than the maximum recommended human dose in adults and 7- and 17-times higher than in a 6-year old child.

Pharmacokinetics

As noted in previous reports, mannitol is rapidly absorbed to the systemic circulation following inhalation in laboratory animal species and humans; the plasma half-life is short. Bioavailability by the inhalational route in humans was 96% of the oral bioavailability; the absolute oral bioavailability was about 20%. Mannitol is fairly extensively metabolised after oral administration (by gut microflora) but little metabolism is observed following intravenous (IV) administration.

Relative exposure

Due to absent/limited toxicokinetic data, animal:human exposure ratios for mannitol have been calculated based on body surface area-adjusted doses for consideration of systemic toxicity and mg/kg doses for consideration of local effects on respiratory tissues (Table 1). The same maximum recommended human dose (800 mg/day) applies to adults and children (≥ 6 years old).

² Kishioka C, Okamoto K, Kim JS, Rubin BK. Hyperosmolar solutions stimulate mucus secretion in the ferret trachea. *Lab and Animal Invest* 2003; 124:306–313.

³ Chen BT, Yeates DB. Ion transport and regulation of respiratory tract fluid output in dogs. *J Appl Physiol* 2001; 90:821–831.

⁴ Peatfield AC, Richardson PS, Wells UM. The effect of airflow on mucus secretion into the trachea of the cat. *J Physiol* 1986; 380:429–439.

Table 1: Relative Exposures

Study	Species; Treatment duration		Sex	Dose		Relative exposure			
				mg/kg/day	mg/m ² /day	local [based on mg/kg]		systemic [based on mg/m ²]	
						adult	child	adult	child
666958	Rat (SD)	pilot study	M/F	641	3846	40	16	7	4
1124				6744	70	28	13	7	
XIS 002		2 weeks	M	8.4	50	0.5	0.2	0.09	0.05
				23.3	140	1.5	0.6	0.27	0.14
				64.6	388	4.0	1.6	0.7	0.4
			F	9.9	59	0.6	0.25	0.11	0.06
				27.8	167	1.7	0.7	0.32	0.17
				76.5	459	5	2	0.9	0.5
XIS 005		13 weeks	M/F	124	744	8	3	1.4	0.7
				210	1260	13	5	2.4	1.3
666371	Dog (Beagle)	pilot study	M	≤380	≤7600	24	10	14	8
F			≤513	≤10260	32	13	19	10	
666387		2 weeks	M	98	1960	6	2.5	3.7	2.0
				216	4320	14	5	8	4
				834	16680	52	21	32	17
			F	101	2020	6	2.5	3.8	2.0
				285	5700	18	7	11	6
				743	14860	46	19	28	15
667108		26 weeks	M/F	171	3420	11	4	6	3.4
				713	14260	45	18	27	14
Human; (MRHD = 800 mg/day)			adult	16	528	—	—	—	—
			child	40	1000	—	—	—	—

Conversion factors from mg/kg to mg/m² doses used for rats, dogs, human adults (50 kg) and children (20 kg) are 6, 20, 33 and 25, respectively; MRHD = maximum recommended human dose.

Toxicology

Published data on repeat-dose toxicity in mice, rats and monkeys do not show significant toxicities associated with the systemic administration of mannitol. While the systemic toxicity profile of mannitol is well characterised, data on its safety by inhalation are lacking from the literature. The sponsor has therefore conducted studies focused on this aspect with particular regard to local effects on respiratory tract tissues.

In inhalational toxicity studies, physical/chemical and aerodynamic properties of the aerosol, the anatomic characteristics of the respiratory tract and the breathing pattern are the major determinants of aerosol deposition. In particular, particle concentration and size are critical factors in determining

the deposited dose and the ultimate toxic outcome resulting from the inhalational exposure. The mass median aerodynamic diameters (MMADs) for mannitol particles in the submitted studies ranged from 2.4 to 4.7 µm. Mannitol particles in the studies were considered to be fully respirable by dogs, but partly (yet mostly) by rats (limited particularly at the high-dose levels where there is particle aggregation in the aerosol chamber). Estimated inhaled doses reported in the studies were calculated taking this into account.

Acute toxicity

The acute toxicity of mannitol by inhalation was studied in rats at doses ≤ 98 mg/kg/day (1 hour exposure). No deaths occurred. In males at the high-dose level, there was a reduction of body weight gain (42% lower compared with controls) over the 14-day observation period. In these animals, lung/bronchi weight was also decreased (by 24%). There were also some effects on the respiratory tract at the high-dose level (98 mg/kg) in both sexes. These included arterial mural mineralisation in the lung/bronchi (4/10 for the sexes combined), inflammatory cells in the nasal turbinates (4/10) and loss of cilia in the trachea (6/10). Median lethal dose (LD₅₀) values for animals appear in the literature as 22 g/kg in mice and 13.5 g/kg in rats by oral (PO) administration, 7.47 g/kg in mice and 8.69 g/kg in rats by IV administration and 14 g/kg in mice by intraperitoneal (IP) administration.

Repeat-dose toxicity

Inhalational studies of up to 13 weeks duration were conducted in rats and 26 weeks in dogs. There was no mortality at any of the doses tested (up to 1124 mg/kg/day in rats and 834 mg/kg/day in dogs). Significant reductions in body weight gain were observed in female rats in the 13-week study (17–21% lower compared with controls). However, this was not dose related, not seen in male rats and not observed in dogs at higher exposure levels.

Pulmonary effects

In dogs, treatment caused coughing during and immediately post dose in all three studies; the effect was dose related. This is likely to be related to the heavy powder loads being delivered, rather than a sign of mannitol toxicity. In the 26 week study, this mostly occurred early in the treatment phase (about for the first 3 weeks) then reduced down to a minimum as treatment progressed. There was no accompanying effect on respiratory function. Salivation and emesis were also seen early in the 2 and 26 week studies. In the latter study, the incidences were greatest in the first week of treatment, reduced in week 2 and were not observed from the third week of treatment. No treatment related clinical signs were observed in the studies in rats.

Macroscopic and microscopic findings observed in the respiratory tract tissues of rats treated with mannitol were generally consistent with findings also seen in concurrent control animals. Where there were apparent increases, their incidence showed no strong dose relationship. Eosinophilic inclusions in the nasal turbinates were seen to be increased in treated animals compared with controls in the 13 week study, but the incidence in the treated groups was comparable to the control level seen in the earlier 2 week rat study. Alveolitis was somewhat more common in rats treated at 210 mg/kg/day for 13 weeks compared with controls but there was no increase in severity (always minimal). In addition the exposure ratio at this dose is reasonably high (5–13 based on mg/kg doses). Increased inflammatory cells in the lungs and bronchi were noted at the high dose level in the 2 week rat study; this finding was not reproduced in the 13 week study though, even at higher doses.

In dogs, froth filled trachea and spongy lungs were observed in a dose range finding study (up to 380 or 513 mg/kg/day) and at the high dose level (743–834 mg/kg) in the 2-week study but not in the 26-week study (≤ 713 mg/kg/day). There was no histopathological correlate for these findings. Bodyweight-relative lung weight was increased in dogs (by about 15–40%) in the pilot study and at

the high dose level in males in the 2 week study (834 mg/kg/day); this was not found, however, in rats (relative exposure, ≤ 5 compared with children and ≤ 13 compared with adults; 13 week study) or the 26 week dog study (relative exposure, ≤ 18 compared with children and ≤ 45 compared with adults). Alveolitis (in females) and bronchioloalveolitis (in males) were seen to be increased in incidence in treated dogs in the 2 week study but there was no clear dose-relationship nor consistency between sexes or increase in severity and the finding was not reproduced in the 26 week study.

Bronchoalveolar lavage (BAL) cell counts showed no treatment related differences in total white blood cell (WBC) counts or WBC populations in rats after 13 weeks treatment. However in dogs, some increases in total WBC counts were evident after 2 and 26 weeks dosing although these were not dose dependent or statistically significant. As a percentage of total WBC, neutrophils increased in dogs treated with mannitol for 26 weeks; this occurred in both sexes and at both dose levels and the increase was dose related. Following a 4 week recovery period, total WBC cells were no longer elevated compared with controls in males while they appeared not to change in high dose females (reversibility was not assessed at the low dose level). However, the population of each WBC type (including neutrophils) returned to normal. The increase in neutrophils in BAL fluid seen in dogs might represent a non-specific immunological response to high powder loads (rather than specific mannitol toxicity) and dogs were more sensitive than rats to this response.

Overall, the absence of significant, clearly treatment related respiratory tract findings in rats and dogs following dosing with mannitol by inhalation at considerable multiples of the human dose (≤ 5 in rats and ≤ 18 in dogs compared with children and ≤ 13 and ≤ 45 in the respective species compared with adults in the longest studies; based on mg/kg doses) suggests no toxicologically significant effects on the lungs of patients treated with Bronchitol.

Systemic effects

Increases in findings of congestion, plasmacytosis and haemorrhage in the mandibular lymph nodes (which are close to the portal of entry of the test compound) were observed following administration of mannitol by inhalation at a dose of 210 mg/kg/day in the 13 week rat study. This may have caused an increase in peripheral blood lymphocytes observed in both sexes at Week 6. However, these cell numbers were within the laboratory historical control values and decreased by Week 13 despite continued treatment. The incidences of plasmacytosis and haemorrhage in the mandibular lymph nodes were relatively high in control animals in this study. Similar findings were also noted in the 26-week dog study. In this study, mandibular lymph nodes were enlarged (2/4) and lymphadenitis and erythrophagocytosis observed (1/4 for each) in the female high-dose group (716 mg/kg/day); male animals showed no such changes (≤ 710 mg/kg/day). Unlike in the rat study, there were no changes in lymphocyte parameters in the circulating blood (analysed by both haematology and flow cytometry). The changes found in the mandibular lymph nodes in the rat and dog studies are considered of minor toxicological significance and likely to have arisen spontaneously or from high local concentrations of mannitol powder.

Osmotic diuretics like mannitol are associated with electrolyte imbalance at high doses. In the data provided, there were some changes in plasma electrolytes in rats and dogs. However, these effects were modest and some were not consistently observed across the dosing period. No significant changes in urinalysis parameters were observed in either rats or dogs (relative exposure, ≤ 1.3 and ≤ 17 in the respective species compared with a child, and ≤ 2.4 and ≤ 32 compared with an adult; based on body surface area-adjusted doses). In addition, there were no treatment related findings in the kidneys of dogs identified in the macroscopic and histopathological examinations. There was an increased incidence of inflammatory cells in the interstitial area of the kidney observed in high-dose male rats in the 13 week study, although this finding is considered likely to be incidental.

In summary, there were no major toxicities found in rats and dogs after inhalation of mannitol for up to 13 and 26 weeks, respectively. At 13 weeks, the duration of the longest rodent study is shorter than the 26 weeks recommended under International Conference on Harmonisation (ICH) guidelines to support chronic use in humans. However, this is not considered to be a major deficiency of the package given the lack of significant effects in the 13 week rat study and that no increase in toxicity with continued dosing was apparent in that study compared to the 2 week rat study, nor in the studies in dogs.

Genotoxicity

Extensive published data establish that mannitol is not genotoxic. In Good Laboratory Practice (GLP) compliant studies conducted by the National Toxicology Program (NTP), U.S. Department of Health and Human Services, mannitol was not mutagenic in the bacterial reverse mutation assay, not mutagenic in the mouse lymphoma/TK^{+/−} assay, negative in the sex-linked recessive lethal mutation test in *Drosophila*, negative in the sister chromatid exchange assay in Chinese Hamster Ovary (CHO) cells, and not clastogenic in the mouse bone marrow micronucleus test (involving IP doses of mannitol up to 3000 mg/kg/day for 3 consecutive days). Negative results are also reported for the compound in additional Ames tests (Fujita *et al.*, 1988; Prival *et al.*, 1991), *in vitro* clastogenicity assays in CHO, CHL and mouse lymphoma L5178Y cells (Aardema *et al.*, 2006; Lorge *et al.*, 2006; Oliver *et al.*, 2006; Wakata *et al.*, 2006), a *Drosophila* embryonic cell culture test (Bournias-Vandiabasis *et al.*, 1983); a transformation assay using A-31-1-13 BALB/c-3T3 cells (Matthews *et al.*, 1993) and the dominant lethal assay in rat (IPCS, 1987).^{5,6,7,8,9,10,11,12,13}

Carcinogenicity

No carcinogenicity studies have been conducted with inhaled mannitol. Published literature was provided to support that mannitol is not carcinogenic by the oral route.

Mannitol fed to male and female Wistar rats at doses of 4.4 and 5.2 g/kg, respectively (10% in diet), for a period of 104–107 weeks did not result in significant increases in tumour incidence (Lina *et al.*, 1996).¹⁴ Similarly, mannitol was not carcinogenic to F344/N rats and B6C3F₁ mice given doses

⁵ Fujita H, Nakano M, Sasaki M. Mutagenicity test of food additives with *Salmonella typhimurium* TA 97 and TA 102. III. Kenkyu Nenpo-Tokyo-Toritsu Eisei Kenkynsho 1988; 39: 343–350.

⁶ Prival MJ, Simmon VF, Mortelmans KE. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. *Mutat Res* 1991; 260: 321–329.

⁷ Aardema MJ, Snyder RD, Spicer C, et al. SFTG international collaborative study on *in vitro* micronucleus test III. Using CHO cells. *Mutat Res* 2006; 607: 61–87.

⁸ Lorge E, Thybaud V, Aardema MJ, et al. SFTG international collaborative study on *in vitro* micronucleus test I. General conditions and overall conclusions of the study. *Mutat Res* 2006; 607: 13–36.

⁹ Oliver J, Meunier JR, Awogi T, et al. SFTG international collaborative study on *in vitro* micronucleus test V. Using L5178Y cells. *Mutat Res* 2006; 607: 125–152.

¹⁰ Wakata A, Matsuoka A, Yamakage K, et al. SFTG international collaborative study on *in vitro* micronucleus test IV. Using CHL cells. *Mutat Res* 2006; 607: 88–124.

¹¹ Bournias-Vandiabasis N, Teplitz RL, Chernoff GF, Seecof RL. Detection of teratogens in the *Drosophila* embryonic cell culture test — Assay of 100 chemicals. *Teratology* 1983; 28: 109–122.

¹² Matthews EJ, Spaling JW, Tennart RW. Transformation of BALB/c-3T3 Cells: V. Transformation responses of 168 chemicals compared with mutagenicity in *Salmonella* and carcinogenicity in rodent bioassays. *Environ Health Persp* 1993; 101 (Suppl 2): 347–482.

¹³ International Programme of Chemical Safety (IPCS) report on WHO Food Additives Series 21 – Mannitol. (1987) <http://www.inchem.org/documents/jecfa/jecmono/v21je10.htm>.

¹⁴ Lina BAR, Bos-Kuijpers MHM, Til HP, Bär A. Chronic toxicity and carcinogenicity study of erythritol in rats. *Regul Toxicol Pharm* 1996; 24: S264–S279.

of 2.5% and 5% in food for 103 weeks (NTP, 1982; Abdo *et al.*, 1986).^{15,16} The only effects that could be attributed to the mannitol administration were the increased incidences of mild nephrosis (focal vacuolisation of renal tubular epithelium) in both sexes of mice and dilatation of the gastric fundal gland in female rats. In addition, administration of mannitol to transgenic mice (C57BL/6 mice p53+/-) at a dose of 5% in food for 26 weeks did not produce any neoplasms in the animals (Iatropoulos *et al.*, 2001).¹⁷ This compound was also tested on transgenic DNA repair deficit Xpa-/- mice and double transgenic Xpa-/-p53+/- mice (with enhanced sensitivity to carcinogens). In this study, mannitol fed at doses of up to 10% in food for 9 months was not carcinogenic (Lina *et al.*, 2004; equivalent to about 16 and 20 g/kg/day for males and females, respectively).¹⁸

The sponsor provided the following reasons to support the relevance of the oral carcinogenicity data and the conclusion that mannitol is unlikely to have carcinogenic potential by the inhalational route:

- the low clinical doses to be given by inhalation as compared with PO and IV;
- a significant proportion of an inhaled dose is swallowed;
- single- and repeat-dose inhalation studies have shown no evidence of respiratory tract irritancy in rats or dogs;
- mannitol is devoid of mutagenic and clastogenic activity;
- mannitol is relatively soluble, thus easily cleared from the respiratory tract;
- the half-life in the lung is quoted at 26.5 minutes and the elimination half-life in serum is about 100 minutes; and
- a small percentage of systemically absorbed mannitol undergoes hepatic metabolism and it is primarily excreted unchanged in the urine.

The sponsor's justifications and conclusion were accepted; the absence of carcinogenicity data for mannitol by the inhalational route was not considered to be a deficiency of the application.

Reproductive toxicity

No reproductive toxicity data on inhaled mannitol were provided.

In the published literature, IV administration of mannitol to pregnant rats at a dose of about 150 mg/kg/day from Day 6 to 15 of gestation did not result in any treatment related effects in dams or in fetuses (Chung *et al.*, 2005).¹⁹ In another study, Desesso *et al.* (1994) reported that fetuses of pregnant rabbits that received a single subcutaneous (SC) dose of mannitol (550 mg/kg) on Gestation Day 12 did not show developmental toxicity.²⁰ In an *in vitro* study, mannitol at concentrations up to 40 mM did not affect chick embryo neural retina cell aggregation, growth or

¹⁵ National Toxicology Program (NTP) (1982) Carcinogenesis bioassay of D-mannitol (CAS No. 69-65-8) in F344/N Rats and B6C3F₁ Mice (Feed Study). TR-236.

¹⁶ Abdo KM, Huff JE, Haseman JK, Alden CJ. No evidence of carcinogenicity of D-mannitol and propyl gallate in F344 rats of B6C3F₁ mice. Food Chem Tox 1986; 24: 1091–1097.

¹⁷ Iatropoulos MJ, Jeffrey AM, Schlüter G, Enzmann HG, Williams GM. Bioassay of mannitol and caprolactam and assessment of response to diethylnitrosamine in heterozygous p53-deficient (+/-) and wild type (+/+) mice. Arch Toxicol 2001; 75: 52–58.

¹⁸ Lina BAR, Woutersen RA, Bruijntjes JP, et al. Evaluation of the Xpa-deficient transgenic mouse model for short-term carcinogenicity testing: 9-month studies with haloperidol, reserpine, phenacetin, and D-mannitol. Toxicol Pathol 2004; 32: 192–201.

¹⁹ Chung MK, Kim JC, Han SS. Embryotoxic effects of CKD-602, a new camptothecin anticancer agent, in rats. Reprod Toxicol 2005; 20: 165–173.

²⁰ Desesso JM, Scialli AR, Goeringer GC. D-Mannitol, a specific hydroxyl free radical scavenger, reduces the developmental toxicity of hydroxyurea in rabbits. Teratology 1994; 49: 248–259.

differentiation (Daston *et al.*, 1991).²¹ In addition, it was reported that mannitol had no effect on fetal survival and was not teratogenic at oral doses of up to 1.6 g/kg/day for 10 days in pregnant mice and rats and up to 1.2 g/kg/day for 5 days in hamsters, although gestation stages were not clearly stated (IPCS, 1987).¹³ Studies examining the effect of mannitol on fertility and postnatal development were not identified in the literature.

The existing data suggest that Bronchitol is unlikely to cause reproductive toxicity. Furthermore, the draft PI contains a cautionary statement against use during pregnancy. Therefore, the absence of this toxicity data is acceptable.

Pregnancy Category B2 has been proposed for this product. This matches the existing categorisation for Aridol and is considered appropriate given the lack of data for the inhalational route and the absence of fetal damage observed in studies by other routes.

Use in children

No studies have been conducted with mannitol in juvenile animals to support the paediatric use of Bronchitol. This is acceptable and consistent with the relevant TGA-adopted EU guideline on nonclinical testing of juvenile animals, given the existing data available.²² Studies in adult animals have not identified target organ toxicity involving developing systems (and general development of the pulmonary system is complete at the proposed patient ages [≥ 6 years]). Aridol is approved for use in children ≥ 6 years old.

Local tolerance

Mannitol was not an ocular irritant in *in vitro* (bovine cornea) or *in vivo* (rabbit) studies.

Nonclinical Summary and Conclusions

Mannitol is a hyperosmotic agent shown to induce mucin secretion in the trachea and increase respiratory tract fluid output in animals.

Inhaled mannitol had no effect on heart rate, ECG, respiratory rate, tidal volume or minute volume in dogs at doses up to 17 and 32 times higher than the maximum recommended human dose in a 6 year old child and an adult, respectively, adjusted for body surface area. Similarly, inhalation of mannitol did not cause signs of CNS toxicity in either rats or dogs at relative exposure levels up to 7–32.

Published data show no significant systemic toxic effects of mannitol in mice, rats and monkeys. No major toxicities were found in rats and dogs after daily inhalational administration of mannitol (for up to 13 and 26 weeks in the respective species) at considerable multiples of the clinical dose in adults (13 in rats and 45 in dogs) and children (5 and 18, respectively) on a mg/kg basis, indicating that pulmonary toxicity is unlikely to be encountered in patients. There were some respiratory tract findings in treated animals but these were of minor severity and/or did not show a clear relationship to treatment (based on absence of dose relationships and lack of reproducibility across sexes/studies). The most notable finding was a dose-related cough in dogs during and immediately after dosing, and this is likely to be related to the heavy powder loads being delivered. This mostly occurred in the early stages of treatment (about the first 3 weeks) and reduced as treatment progressed. Accompanying salivation and emesis were also often observed. Increases in bronchoalveolar lavage (BAL) white blood cell count and percentage neutrophils were observed in dogs. This is considered likely to reflect a non-specific immunological response to high powder

²¹ Daston GP, Baines D, Yonker JE. Chick embryo neural retina cell culture as a screen for developmental toxicity. *Toxicol Appl Pharmacol* 1991; 109:352–366.

²² EMEA. Committee for Medicinal Products for Human Use (CHMP), 29 September 2005. Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications, CHMP/SWP/169215/2005.

loads (rather than specific mannitol toxicity); it did not attain statistical significance and was not seen in rats.

Mannitol is not genotoxic, and the compound has been shown not to be carcinogenic in mice and rats when administered in the diet. The sponsor has provided an adequate justification for the absence of carcinogenicity studies utilising the inhalational route.

Published animal data indicate that mannitol is not embryotoxic or teratogenic.

There were no nonclinical objections to the registration of Bronchitol for the proposed indication.

IV. Clinical Findings

Pharmacokinetics

Introduction

There were two clinical studies of pharmacokinetics, one in healthy volunteers (Study DPM-PK-101) and one in subjects with CF (DPM-PK-102). In addition there were two studies of inspiratory flow rates when using dry powder inhaler devices (Studies DPM-OSM-401 and DPM-OSM-403).

Study DPM-PK-101

Study DPM-PK-101 was a single centre, randomised, open-label, three-way, crossover pharmacokinetic study in healthy adult volunteers. The study included 18 healthy male volunteers aged 19 to 48 years, with no history of asthma or other chronic diseases which could compromise the airways or gut absorption. Hypothesis tests were not performed. All subjects received at screening a dose of 635 mg mannitol by inhalation. This was followed, in random order and separated by washout, by the three treatments:

Test: mannitol 635 mg by inhalation (Aridol)

Reference:

1. mannitol 500 mg in 50 mL water administered orally
2. mannitol 500 mg as a 10% solution administered intravenously

The mean (SD) absolute bioavailability of the inhaled mannitol was 0.591 (0.146). This was similar to the absolute bioavailability of oral mannitol which was 0.625 (0.142). Pharmacokinetic data are shown in Table 2.

Table 2: Pharmacokinetics data for mannitol in Study DPM-PK-101

	T_{max} (hr)	C_{max} (ng/ml)	t_{1/2} (hr)	AUC₀₋₂₄ (ng.hr/ml)	AUC_{0-inf} (ng/hr.ml)	BAV	CL (ml/hr)	CL_R (ml/hr)	V_D (L)
Inhalation									
Mean	1.5	10792*	4.7	56265*	57599*	0.591			
S.D	0.5	2638	1.0	12586	12717	0.146			
Oral									
Mean	1.4	13094	5.2	59776	61414	0.625			
S.D	0.5	3085	1.1	13596	14059	0.142			
Intravenous									
Mean	0.11	44322	4.5	98719	100236	1.000	5099	4439	34.3
S.D	0.04	8775	1.1	21735	21561		989	1143	13.8

*values were dose-normalised to 500 mg dose

Study DPM-PK-102

Study DPM-PK-102 was a multicentre, open-label, single and multiple dose study to estimate systemic mannitol pharmacokinetics of inhaled dry powder mannitol at 400 mg in subjects with cystic fibrosis. The treatment was mannitol powder for inhalation 400 mg twice daily for 7 days,

except for Days 1 and 7 when administration was once only in the morning. The study included nine subjects: six adult subjects (three male, three female, age range 18 to 32 years) and three adolescents (2 male 1 female, age range 12 to 17 years) all of whom completed the trial. The pharmacokinetic parameters were similar for the two age groups, and for multiple compared with single dosing (Table 3). There did not appear to be significant accumulation of mannitol with multiple dosing.

Table 3: Pharmacokinetics data for mannitol in Study DPM-PK-102

Age group/Dose Day		C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-12h} (hr*ng/mL)	Kel (1/hr)	AUC _{0-infinity} (hr*ng/mL)	t _{1/2} (hr)
Adult (n=6)	Day 1	7670 (1175)	2.42 (1.07)	41844 (4935)	0.116 (0.02)	50445 (9498)	6.10 (1.15)
	Day 7	9260 (2718)	1.37 (0.30)	50248 (13597)	0.129 (0.013)	59687 (11315)	5.42 (0.59)
Adolescents (n=3)	Day 1	8017 (2967)	1.84 (1.05)	38417 (6694)	0.098 (0.020)	48305 (5758)	7.29 (1.65)
	Day 7	7667 (2021)	1.83 (0.29)	45896 (8681)	0.106 (0.003)	57205 (9778)	6.52 (0.18)

Study DPM-OSM-401

Study DPM-OSM-401 was an open label, observational, non-drug study of inspirational flow rates and volumes in subjects using the Osmohaler dry powder inhaler device. The study tested the Osmohaler device and no medications were involved. The study included 34 asthmatic and healthy control subjects aged 6 to 69 years, with a baseline FEV₁ ≥70% of predicted value. There were 14 children aged 6 to 10 years (ten asthmatic), nine adolescents aged 11 to 17 years (seven asthmatic) and eleven adults (eight asthmatic). There were 22 (64.7%) male subjects and 12 (35.3%) female. The study concluded that there were adequate flow rates to ensure operability of the device in all the age groups.

Study DPM-OSM-403

Study DPM-OSM-403 was an open label, observation, non-interventional study of inspiratory flow rates and volumes in subjects with cystic fibrosis inhaling via a spirometer with the high resistance RS01 dry powder inhaler device in series. The study tested the RS01 dry powder inhaler device and no medications were involved. The study included subjects with confirmed cystic fibrosis with baseline FEV₁ ≥30% and <90% of predicted value. A total of 26 subjects enrolled were enrolled and 25 completed. Fifteen (60%) subjects were female and ten (40%) were male; 24 (96.0%) were Caucasian and the age range was 6 to 37 years. The investigators concluded that subjects with baseline FEV₁ >1L would be able to generate sufficient flow rates to adequately use the device but subjects with FEV₁ ≤1L might not be able to generate sufficient flow rates with a single inhalation and might require repeated deep inhalations to deliver the dose.

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic studies did not have sufficient sample sizes to enable hypothesis testing. However, the results indicate that mannitol by inhalation has similar bioavailability to oral mannitol, and that there does not appear to be accumulation with multiple dosing. The studies of the dry powder inhalers indicated the feasibility of delivering Bronchitol using such devices.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Efficacy

Introduction

Data from one Phase III pivotal study (Study DPM-CF-301) and three Phase II studies (Studies DPM-CF-201, DPM-CF-202 and DPM-CF-203) conducted in subjects with CF were included in the submission.

Supporting Studies

Study DPM-CF-201

Study DPM-CF-201 was a multicentre, double blind, randomised, crossover controlled Phase II trial which appeared to have been conducted as a proof of concept trial. The study was conducted at eight study sites in Australia and New Zealand. The study included subjects with:

- Confirmed diagnosis of cystic fibrosis
- Age ≥ 8 years
- FEV₁ between 40% and 80% of predicted for age, height and gender, or a decrease in FEV₁ of 20% or more than that recorded 6 to 12 months previously
- Clinically stable

The study treatments were:

1. Bronchitol 30 mg, 14 capsules, twice daily. Average particle diameter 3 microns, fine fraction greater than 40%
2. Placebo: Crystalline mannitol, average particle diameter 68 microns, fine particle fraction <2%.

Subjects were randomised to treatment using a randomisation schedule. A bronchodilator was administered 15 minutes prior to treatment. Both treatments were administered using the RS01 dry powder inhaler device. At the beginning of the study all subjects underwent a bronchial provocation test using small but increasing doses of Bronchitol. There was a washout of 2 weeks between treatments. There were two treatment periods of 2 weeks.

The primary efficacy outcome measure was FEV₁. The secondary efficacy outcome measures were:

- Spirometry
- Quality of Life
- Sputum microbiology
- Sputum rheology
- Safety profile

The initial sample size calculation was based on a mean difference of 8% FEV₁ % predicted, a population standard deviation of 20% and a 15% dropout rate. This was modified following a blinded analysis of the standard deviation (SD) of FEV₁ for the population. The initially planned sample size of 60 was reduced to 39.

A total of 49 subjects were enrolled in the study and 39 subjects were randomised to treatment and analysed. During the study 38 subjects were exposed to Bronchitol and 36 to control. The age range was 8 to 48 years, 23 (59%) subjects were female and 16 (41%) were male.

- There was a 7% improvement in FEV₁ following Bronchitol and no change following placebo (p=0.008).
- There was a significant increase of approximately 15% in the forced expiratory flow in middle half of an expiration (FEF₂₅₋₇₅) with Bronchitol (p<0.01)

- There was a slight increase of approximately 2% in FEV₁/forced vital capacity (FVC) ratio (p<0.05).
- There was no significant change in FVC or peak expiratory flow rate (PEFR).
- Overall there was no significant change in Quality of Life scores.
- Respiratory symptom scores improved with Bronchitol.
- There was a gain of pathogen growth in four (15.4%) subjects in the Bronchitol group compared with one (3.9%) in the control.
- Sputum rheology data were not included in the report.

Study DPM-CF-202

Study DPM-CF-202 was a multicentre, open label, randomised, crossover dose-finding Phase II study. The study was conducted at 12 sites in two countries: Canada (seven sites) and Argentina (five sites). The study included subjects with:

- Diagnosis of cystic fibrosis
- Age ≥ 7 years
- FEV₁ between 40% and 90% of predicted for height, age and gender
- Able to perform acceptable quality spirometry

The exclusion criteria included:

- Currently active asthma
- Colonised with *Burkholderia cepacia* or methicillin-resistant *Staphylococcus aureus* (MRSA)
- Requiring home oxygen or assisted ventilation
- Current illness that in the investigators' opinion may contribute to an increased and unacceptable risk if the subject were enrolled (for example, significant varices, portal hypertension, cor pulmonale)
- Significant episode of haemoptysis (>60 mL) in the past 12 months
- Concurrent use of beta-blocker medication
- Concurrent use of hypertonic saline

The study treatments were: Bronchitol for inhalation, initially 400 mg twice daily for two weeks then in random order: 40 mg, 120 mg and 240 mg each for two weeks. The study duration was for 13 weeks in total: four two week administration periods each followed by one week washout periods. There was no reference therapy. There was twice daily administration, the treatments were delivered via the Osmohaler device and salbutamol was administered prior to each treatment. Treatment allocation was performed using sequential study numbers and a randomisation schedule.

The primary efficacy outcome variables were the change between pre- and post-dose FEV₁ and FVC. The secondary efficacy outcome variables were: spirometry, sputum samples, Cystic Fibrosis Questionnaire – Revised (CFQ-R) and respiratory symptoms. The sample size calculation assumed an SD of 6% and a precision of 2% in order to determine a sample size of 36 subjects not being treated with rhDNase. Assuming dropout/missing variable for six subjects, a final sample size of 42 subjects was determined.

A total of 85 subjects were enrolled, all of whom were included in the safety analysis. Of these subjects, eight did not meet eligibility criteria, 27 failed the Aridol challenge and two withdrew prior to treatment. Forty eight subjects were randomised to treatment and were included in the intention to treat population. Age range was 7 to 68 years, 26 (54.2%) were male, and 22 (45.8%) were female. Forty (83.3%) subjects were Caucasian and seven (14.6%) were Hispanic. Mean

(SD) height was 153.0 (16.78) cm, weight was 48.0 (18.71) kg, body mass index (BMI) was 19.6 (4.41) kg/m², FEV₁ was 1.86 (0.645) L and % predicted FEV₁ was 64.14 (13.182) %.

- The improvement in FEV₁ was greatest with the 400 mg dose. Although there was no statistically significant difference between 400 mg and either 120 mg or 240 mg, there was clearly no plateau of effect.
- There were similar findings for FVC.
- There was no significant difference between the doses in FEV₁/FVC.
- There was a plateau in effect on FEF₂₅₋₇₅ from the 120 mg dose level.
- There was no indication of a plateau of effect on PEF, although the differences between the treatments were not statistically significant.
- There did not appear to be any effects of dose on sputum microbiology but the duration of treatment may not have been long enough for such effects to manifest. Sputum weight decreased to a greater degree with increasing dose.
- Quality of life for respiratory domain improved to the greatest extent in the 400 mg dose, with no indication of plateaux of effect.

Study DPM-CF-203

Study DPM-CF-203 was an open label, multicentre, randomised crossover, comparative Phase II study of inhaled mannitol alone and in combination with rhDNase compared with rhDNase. The study was conducted at two centres in the UK. The study included subjects with:

- Confirmed diagnosis of CF by sweat test and/or genotype
- Age between 8 and 19 years
- FEV₁ <70% predicted for height, age and gender
- Eligible to receive rhDNase or currently taking rhDNase for at least 4 weeks
- Able to perform acceptable quality spirometry
- Clinical condition is stable in the week prior to study entry
- Not administered additional antibiotics or oral steroids for 14 days prior to study entry

The exclusion criteria included:

- Currently active asthma
- Colonisation with *Burkholderia cepacia* or MRSA
- Considered “terminally ill” or listed for transplantation
- Required home oxygen or assisted ventilation
- Significant episode of haemoptysis (>60 mL) in the previous 12 months
- Known aortic or cerebral aneurysm
- Uncontrolled hypertension; systolic blood pressure (BP) >200 mmHg or diastolic BP >100 mmHg

The study treatments were:

1. Mannitol 400 mg twice daily
2. Mannitol 400 mg twice daily and rhDNase 2.5 mg once daily
3. rhDNase 2.5 mg once daily

Mannitol was administered by dry powder inhaler and rhDNase was administered by nebulizer. Randomisation to treatment sequence was in balanced blocks by centre. Treatment was preceded by a mannitol tolerance test for airway hyper-reactivity.

The primary efficacy outcome measure was change in FEV₁. Secondary outcome measures were: FVC, FEF₂₅₋₇₅, oxygen saturation, visual analog score (VAS) with exercise, quality of life (QOL), respiratory symptoms, sputum microbiology and cytokines. Safety was assessed by adverse effects (AEs). Forty two subjects were required to complete the study to achieve a power of 90% and an alpha of 0.05. Assuming a 15% dropout rate the intended sample size was 48 subjects.

A total of 40 subjects were recruited, 28 were randomised and 26 received study drug which is less than the intended sample size. All 26 subjects who received treatment were included in the intent-to-treat (ITT) population. The age range was 9 to 17 years, 17 (65.4%) subjects were female, nine (34.6%) were male; mean (SD) weight was 41.9 (10.78) kg, height was 151.2 (14.19) cm, BMI was 18.0 (2.17) kg/m², FEV₁ was 1.782 (0.5851) L; and all subjects were Caucasian.

- There were no significant differences between the treatment arms in any of the outcome measures. However, although there appeared to be improvements in FEV₁ in the mannitol and rhDNase alone groups, there was no improvement in the mannitol/rhDNase group. This suggests there might be an interaction between the treatments with cancelling of effect.
- The results for FVC were similar.
- There did not appear to be effects on FEV₁/FVC.
- FEF₂₅₋₇₅ appeared to improve with all three treatment arms.
- PEF also suggested a cancelling of effect as an interaction.
- There were no significant differences between treatments in quality of life scores, sputum microbiology or respiratory symptom scores. The small sample size and open nature of the trial would also make QOL and symptom scores difficult to interpret.

Study DPM-CF-301 (Pivotal Study)

Study Details

Study DPM-CF-301 was a multicentre, randomised, double blind, placebo controlled, parallel group Phase III study of efficacy and safety. The study comprised a double blind phase of 6 months duration followed by an open label phase for 6 months. The study was conducted at 40 sites in 4 countries: Australia (10), New Zealand (2), United Kingdom (24), and Ireland (4).

The inclusion criteria included:

- Confirmed diagnosis of cystic fibrosis
- Aged ≥6 years
- FEV₁ ≥30% and ≤90% predicted
- Able to perform all the techniques necessary to perform lung function

The exclusion criteria included:

- Considered “terminally ill” or listed for lung transplantation
- Have had a lung transplant
- Be using nebulised hypertonic saline
- Have had a significant episode of haemoptysis (>60 mL) in the 3 months prior to enrolment
- Have had a myocardial infarction; a cerebrovascular accident; major ocular surgery; or major abdominal, chest or brain surgery in the three months prior to enrolment
- Have a known cerebral, aortic or abdominal aneurysm
- Breast feeding, pregnant or planning to become pregnant during the study
- Using beta-blockers
- Uncontrolled hypertension – systolic BP >190 and/or diastolic BP >100 mmHg

- Have a condition or be in a situation which in the investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the subject's participation in the study
- Mannitol tolerance test (MTT) test positive

The study treatments during the double blind phase were:

1. Mannitol, 40 mg, 10 x 40 mg capsules twice daily
2. GMP dry powdered mannitol for inhalation at a sub-therapeutic dose, 10 x 5 mg capsules twice daily

During the open label phase all subjects received mannitol 400 mg twice daily. Treatments were administered by dry powder inhaler, 5 second breath hold post inhalation after each capsule. Treatments were preceded by salbutamol 400 µg. Physiotherapy followed study treatment and preceded rhDNase.

The primary efficacy outcome measure was the change from baseline in FEV₁. Secondary efficacy outcome measures were:

- FEV₁ for the rhDNase subgroups
- FEV₁ responder analysis (responders at 26 weeks were those subjects with a mean improvement from baseline of ≥ 100 mL, or $\geq 5\%$ relative to baseline or $\geq 5\%$ relative change in % predicted)
- Pulmonary exacerbations
- Quality of life measured using CFQ-R
- Rescue antibiotic use
- FVC
- FEF₂₅₋₇₅
- Days in hospital for pulmonary exacerbations

A protocol defined pulmonary exacerbation (PDPE) was defined as treatment with intravenous antibiotics for four or more of the following 12 signs or symptoms:

1. Change in sputum production (volume, colour, consistency)
2. Dyspnoea
3. New or increasing haemoptysis
4. Malaise, fatigue or lethargy
5. Fever $\geq 38^{\circ}\text{C}$
6. Anorexia or weight loss
7. Sinus pain or tenderness
8. Change in sinus discharge
9. FVC or FEV₁ decreased by $\geq 10\%$ from previous recorded value
10. Radiographic signs indicative of pulmonary infection
11. Increased cough
12. Changes in physical examination of the chest

Safety endpoints were: AEs, laboratory tests, sputum microbiology, bronchodilator response and physical examination. Efficacy and safety variables were measured at Visit 1 (Week 0) and at Weeks 6, 14 and 26.

Statistical Considerations

Hypothesis tests were performed using mixed models, logistic regression, and negative binomial regression models. The mixed models adjusted for baseline variables: FEV₁, disease severity, age, gender and rhDNase use.

Sample size calculations were based on the primary and secondary objectives of:

- Effect on FEV₁ in the combined group (primary efficacy outcome measure)
- Effect on FEV₁ in subjects taking rhDNase
- Change in exacerbation rates

The calculations assumed a 20% drop out rate and that 2/3 of subjects would be taking concurrent rhDNase, pulmonary exacerbation rates of 0.42 per subject year in the mannitol group and 0.96 per subject year in the control. The sample size calculations estimated 80% power to detect a difference of 70 mL in change in FEV₁ from baseline with 340 subjects in the ratio 3:2 (mannitol: control).

The difference in FEV₁ used to calculate the sample size varied between different versions of the protocol from 120 mL in the Version 1, and 85 mL in Version 4 to that used in the final protocol. In Version 1 the sample size calculation was 80 subjects per arm giving a power of 97% to detect a difference of 120 mL in change from baseline in FEV₁. In Version 4, 109 subjects in the mannitol arm and 73 in the control resulted in 80% power to detect a difference of 85 mL.

Results

A total of 389 subjects were enrolled, 324 were randomised and 295 were included in the ITT population. The ITT population comprised all subjects who were randomised and received at least one dose of study medication. A total of 198 (61.1%) subjects completed the 26 week double blind treatment phase, including 112 (58.3%) in the mannitol group and 68 (65.2%) in the control. The treatment groups were similar in demographic characteristics, the treatment groups for the subgroup of rhDNase users and the treatment groups for the subgroup of rhDNase non-users were also similar in demographic characteristics. In the ITT group there were 165 (55.3%) male subjects, 132 (44.7%) females and the age range was 6 to 56 years. The treatment groups were similar in past medical history. A greater proportion of subjects in the control group had sputum cultures with *Pseudomonas* and *Staphylococcus* species at baseline, and a greater proportion of the mannitol group had *Aspergillus*. There was greater usage of formoterol in the control group, but otherwise concomitant medication use at baseline was similar for the two treatment groups.

For the primary efficacy outcome variable there was a statistically significant treatment benefit in the mannitol group, with the mean (95% Confidence Interval [CI]) treatment effect across all time points being 54.17 (24.73 to 83.60) mL, $p < 0.0001$. The unadjusted results were more favourable for mannitol. The overall treatment effect for rhDNase users was 53.82 (14.03 to 93.61) mL, $p = 0.008$. The overall treatment effect for rhDNase non-users was 54.54 (10.85 to 98.23) mL, $p = 0.015$. These represented a relative improvement in FEV₁ at 26 weeks of 4.11% for the ITT population, 5.11% for rhDNase users and 2.68% for rhDNase non-users. The FEV₁ responder analysis indicated benefit in the ITT population and rhDNase users but not in rhDNase non-users (Table 4). There was no interaction effect with bronchodilator reversibility or *Burkholderia cepacia* colonisation. The treatment effect was not affected by age group.

Table 4: Parameter estimates for the odds of being a responder for subjects treated with mannitol compared with control, completer population

Response Definition	Mannitol [N=116] n (%)	Control [N=89] n (%)	Odds Ratio (95% CI) (Mannitol vs. Control)	p-value
All subjects in completers population				
FEV ₁ absolute increased ¹	62 (53.4)	33 (37.1)	1.97 (1.08, 3.58)	0.026
FEV ₁ percent increase ²	64 (55.2)	36 (40.4)	2.00 (1.09, 3.66)	0.026
FEV ₁ percent predicted increase ³	48 (41.4)	22 (24.7)	2.30 (1.20, 4.38)	0.012
rhDNase users				
FEV ₁ absolute increased ¹	30 (49.2)	12 (24.0)	2.89 (1.21, 6.94)	0.017
FEV ₁ percent increase ²	32 (52.5)	13 (26.0)	3.56 (1.43, 8.87)	0.007
FEV ₁ percent predicted increase ³	23 (37.7)	9 (18.0)	3.11 (1.12, 8.63)	0.029
rhDNase non-users				
FEV ₁ absolute increased ¹	32 (58.2)	21 (53.8)	1.44 (0.59, 3.47)	0.422
FEV ₁ percent increase ²	32 (58.2)	23 (59.0)	1.21 (0.49, 2.96)	0.681
FEV ₁ percent predicted increase ³	25 (45.5)	13 (33.3)	1.89 (0.77, 4.61)	0.165

1 –subject was classified as a responder if the absolute increase in FEV₁ from week 0 to week 26 was ≥ 100 mL.

2 –subject was classified as a responder if the increase in FEV₁ from week 0 to week 26 was $\geq 5\%$ of the baseline value.

3 - subject was classified as a responder if the increase in FEV₁ %predicted from week 0 to week 26 was $\geq 5\%$ of the baseline value.

FVC also improved in the mannitol group relative to control. The mean overall benefit was 70.89 (29.90 to 111.88) mL, $p < 0.001$. At Week 26 there was a treatment benefit of 3.4% relative to baseline, $p = 0.009$. In the rhDNase users there was an average treatment benefit of 70.96 (15.5 to 126.4) mL, $p = 0.012$; and in the non-users this was 70.76 (9.94 to 131.59) mL, $p = 0.023$. There was no significant difference for FEF₂₅₋₇₅, with the mean difference between treatments being 26.54 (-27.15 to 80.23), $p = 0.331$. Hypothesis testing was not performed for PEF or FEV₁/FVC.

There was no significant difference in the incidence rates for PDPE: mean (SD) rate for mannitol 0.78 (1.976) events per subject per year and for control 1.05 (2.148), rate ratio (95% CI) 0.74 (0.47 to 1.18) $p > 0.05$. The proportion of subjects with PDPEs was lower in the mannitol group, 32 (18.1%) subjects, compared with the control, 33 (28.0%) subjects although hypothesis testing was not performed. There was no significant difference in the time to PDPE, $p = 0.115$. Days in hospital due to PDPEs were not experienced by 86% subjects in the mannitol group and 82% in the control group. The difference in mean change in respiratory domain CFQ-R scores at 26 weeks was 3.9 points, in favour of mannitol, but this was not statistically significant, $p > 0.05$. The symptomatology of the PDPE episodes appeared to be similar for the two treatment groups, but no hypothesis tests were performed.

Rescue antibiotic use was not a predefined efficacy outcome measure but was reported. For PDPE all subjects had received antibiotics. For non-protocol defined pulmonary exacerbations (PE), 35.6% subjects in the mannitol group and 50.8% in the control required rescue antibiotics. The rate ratio (95% CI) was reported as 0.73 (0.39 to 1.37), $p = 0.329$. This appears to be a post-hoc analysis.

Safety

Introduction

In addition to the studies discussed above, there were three additional studies submitted in support of safety, all of which were conducted for the indication of bronchiectasis: Studies DPM-B-201, DPM-B-202 and DPM-B-301.

Patient Exposure

In Study DPM-CF-201, 38 subjects were exposed to Bronchitol 420 mg twice daily for two weeks.

In Study DPM-CF-202, 48 subjects were exposed to the 400 mg dose for 2 weeks, and 44 to 40 mg, 120 mg, and 120 mg doses each for 2 weeks duration.

In Study DPM-CF-203, 25 subjects were exposed to mannitol for between 16 and 198 days, with a mean (SD) duration of exposure of 150.20 (50.630) days.

In Study DPM-CF-301, 177 subjects were exposed to mannitol for a mean (SD) duration of 135.5 (70.09) days. A total of 112 (58.3%) subjects were exposed to mannitol for 26 weeks. A total of 63 subjects aged 6-17 years were exposed to mannitol for a mean (SD) duration of 140.9 (66.62) days.

Adverse Events

In Study DPM-CF-201 a total of 27 (71.1%) subjects reported AEs with Bronchitol and 25 (69.4%) with control. The most frequently reported AEs were upper respiratory tract infection (URTI), condition aggravated, cough and nasopharyngitis. There were no clinically significant changes in vital signs.

In Study DPM-CF-202 a total of 187 AEs were reported in 47 (55.3%) subjects. The most commonly reported AEs were: headache (11), condition aggravated (9), pyrexia (8), and pharyngolaryngeal pain (8). No clinically significant changes in vital signs were reported.

In Study DPM-CF-203, AEs were reported in 17 (81%) subjects in the rhDNase, 14 (60.9%) in the Mannitol and 17 (73.9%) in the Mannitol/rhDNase. The commonest AEs were viral URTI and cough.

In Study DPM-CF-301, a total of 822 AEs were reported in 154 (87.0%) subjects in the mannitol group and 541 AEs in 109 (92.4%) subjects in the control. The most commonly reported AEs were: condition aggravated, cough, headache and bacteria sputum identified (Table 5). Haemoptysis, cough, pharyngolaryngeal pain, toothache, vomiting and diarrhoea occurred more commonly in the mannitol group. There were no clinically significant differences between the treatment groups in chest examination findings. Bronchodilator response was similar for the two treatment groups.

Table 5: Most commonly reported treatment emergent AEs by MedDRA preferred term occurring in $\geq 2\%$ in any treatment group during the blinded study period²³

Preferred Term	Mannitol [N=177] n (%)	Control [N=118] n (%)	Total [N=295] n (%)
Condition aggravated	57 (32.2)	42 (35.6)	99 (33.6)
Cough	45 (25.4)	24 (20.3)	69 (23.4)
Headache	38 (21.5)	28 (23.7)	66 (22.4)
Bacteria sputum identified	33 (18.6)	22 (18.6)	55 (18.6)
Nasopharyngitis	25 (14.1)	17 (14.4)	42 (14.2)
Lower respiratory tract infection	15 (8.5)	20 (16.9)	35 (11.9)
Haemoptysis	21 (11.9)	10 (8.5)	31 (10.5)
Pharyngolaryngeal pain	24 (13.6)	5 (4.2)	29 (9.8)
Upper respiratory tract infection	14 (7.9)	8 (6.8)	22 (7.5)
Abdominal pain upper	12 (6.8)	7 (5.9)	19 (6.4)
Arthralgia	12 (6.8)	7 (5.9)	19 (6.4)
Productive cough	12 (6.8)	7 (5.9)	19 (6.4)
Vomiting	13 (7.3)	4 (3.4)	17 (5.8)
Back pain	7 (4.0)	7 (5.9)	14 (4.7)
Abdominal pain	6 (3.4)	8 (6.8)	14 (4.7)
Toothache	9 (5.1)	3 (2.5)	12 (4.1)
Constipation	6 (3.4)	5 (4.2)	11 (3.7)
Diarrhoea	9 (5.1)	1 (0.8)	10 (3.4)
Pyrexia	7 (4.0)	2 (1.7)	9 (3.1)
Fungus sputum test positive	6 (3.4)	3 (2.5)	9 (3.1)
Ear pain	5 (2.8)	4 (3.4)	9 (3.1)
Nausea	4 (2.3)	5 (4.2)	9 (3.1)
Chest discomfort	6 (3.4)	2 (1.7)	8 (2.7)
Tonsillitis	6 (3.4)	2 (1.7)	8 (2.7)
Fatigue	5 (2.8)	3 (2.5)	8 (2.7)
Nasal congestion	4 (2.3)	4 (3.4)	8 (2.7)
Wheezing	4 (2.3)	4 (3.4)	8 (2.7)
Epistaxis	5 (2.8)	2 (1.7)	7 (2.4)
Musculoskeletal chest pain	5 (2.8)	2 (1.7)	7 (2.4)
Rash	4 (2.3)	3 (2.5)	7 (2.4)
Viral infection	3 (1.7)	3 (2.5)	6 (2.0)
Malaise	3 (1.7)	3 (2.5)	6 (2.0)
Oral candidiasis	4 (2.3)	2 (1.7)	6 (2.0)
Pain in extremity	4 (2.3)	2 (1.7)	6 (2.0)
Rhinorrhoea	4 (2.3)	2 (1.7)	6 (2.0)
Asthma	2 (1.1)	3 (2.5)	5 (1.7)
Influenza like illness	4 (2.3)	1 (0.8)	5 (1.7)
Insomnia	4 (2.3)	1 (0.8)	5 (1.7)
Musculoskeletal pain	4 (2.3)	1 (0.8)	5 (1.7)
Sinus headache	4 (2.3)	1 (0.8)	5 (1.7)
Chest pain	1 (0.6)	3 (2.5)	4 (1.4)
Stomach discomfort	1 (0.6)	3 (2.5)	4 (1.4)
Viral upper respiratory tract infection	0 (0.0)	4 (3.4)	4 (1.4)
Rhinitis allergic	0 (0.0)	3 (2.5)	3 (1.0)

²³ MedDRA = Medical Dictionary for Regulatory Activities.

Serious Adverse Events and Deaths

In Study DPM-CF-201 two (13.2%) subjects reported serious adverse events (SAEs) with Bronchitol and two (5.6%) with control. Cough was the only SAE reported in more than one subject.

In Study DPM-CF-202 seven SAEs were reported in five (5.9%) subjects: abdominal pain (1), steatorrhoea (1), condition aggravated (2), malaise (1), headache (1), cough (1).

In Study DPM-CF-203, during mannitol use six SAEs were reported by five (21.7%) subjects, during rhDNase use eight were reported by seven (33.3%) subjects and during mannitol/rhDNase use seven were reported by six (26.1%) subjects. The most commonly reported SAE was exacerbation of cystic fibrosis.

In Study DPM-CF-301, during the 26 week double blind phase 65 SAEs were reported in 46 (26.0%) subjects in the mannitol group and 49 SAEs in 35 (29.7%) subjects in the control. Haemoptysis was more commonly reported as a SAE in the mannitol group, six (3.4%) subjects compared with two (1.7%) in the control.

There were no deaths reported in Study DPM-CF-201, Study DPM-CF-202, Study DPM-CF-203 or Study DPM-CF-301.

Laboratory Findings

In Study DPM-CF-201 no clinically significant changes in laboratory tests were reported. In Study DPM-CF-202, there were no standard haematology, biochemistry or urinalysis tests performed as part of the study. In Study DPM-CF-203, clinical laboratory tests were not provided.

In Study DPM-CF-301, there were no significant differences between the groups in haematology or biochemistry parameters. Sputum microbiology was similar for the two treatment groups. The shift analysis of sputum microbiological findings indicated a slightly higher percentage in the mannitol group shifting from no growth to growth.

Safety in Special Populations

In Study DPM-CF-301, for the subgroup of children aged 6 to 17 years, 57 (90.5%) in the mannitol group and 40 (95.2%) in the control reported AEs. Pharyngolaryngeal pain and diarrhoea were more common in the mannitol group.

Immunological Events

In Study DPM-CF-203, in the rhDNase group there were two reports of hypersensitivity and one of anaphylaxis.

Safety Related to Drug-Drug Interactions and Other Interactions

Study DPM-CF-203 indicates that Bronchitol may cancel out the effects of rhDNase but this was not confirmed in Study DPM-CF-301. In Study DPM-CF-301, rhDNase was administered after mannitol, and after physiotherapy / exercise. This might indicate a need to separate the dosing of the two agents.

Discontinuation Due to Adverse Events

In Study DPM-CF-201, two subjects in the Bronchitol group withdrew because of AEs: lower respiratory tract infection (1) and liver transplant (1). One subject in the control group withdrew because of an AE: condition aggravated (1).

In Study DPM-CF-202 discontinuation due to AE was reported in one subject: bacteria sputum identified.

In Study DPM-CF-203, two (8.7%) subjects in the mannitol group withdrew because of AEs (exacerbation of cystic fibrosis; and cough) and two (8.7%) in the mannitol/rhDNase (nausea; and cough).

In Study DPM-CF-301, 28 (15.8%) subjects in the mannitol group and 10 (8.5%) in the control withdrew because of an AE. The most frequently reported AEs leading to discontinuation were: cough, condition aggravated and haemoptysis. Haemoptysis lead to five subjects discontinuing in the mannitol group and none in the control.

Safety Data from Studies Conducted for Other Indications

Study DPM-B-201 / Study DPM-B-202

Study DPM-B-201 / Study DPM-B-202 were Phase II crossover studies of inhaled dry powder mannitol compared to placebo in subjects with bronchiectasis. The studies were conducted at four sites in Australia and New Zealand. The studies included subjects with: confirmed diagnosis of bronchiectasis (CT scan); aged 15 years or older; with $FEV_1 \geq 1.4$ L and $\geq 50\%$ of predicted for height, age and gender; with chronic cough and excessive secretion of mucous; clinically stable; and able to perform study procedures. The study treatments were:

1. 400 mg mannitol as 10 x 40 mg capsules,
2. Placebo

Treatments were administered twice daily using the Inhalator device. There were two 2 week treatment periods separated by 2 weeks of washout. The safety outcome measures were: spirometry, sputum cultures, and AEs. Efficacy measures were not evaluated because of the different indications for treatment.

A total of 60 subjects were enrolled and received at least one dose of study treatment. Fifty six (93.3%) subjects completed and four (6.7%) withdrew because of AEs. Fifty eight subjects were exposed to Bronchitol. Of the enrolled subjects 41 (68.3%) were female, 19 (31.7%) were male, the age range was 16 to 71 years; mean (SD) height was 166 (8) cm, weight was 68.5 (13) kg, BMI was 20.4 (3.8) kg/m², FEV_1 was 2.4 (0.74) L, % predicted FEV_1 was 87.5 (17.6) %. Bronchitol had little effect on FEV_1 , FVC or sputum microbiology. A total of 103 AEs were reported in 37 (27%) subjects during Bronchitol and 79 in 24 (20%) subjects during placebo. The commonest AEs were: sputum culture positive, lower respiratory tract infection, pharyngolaryngeal pain and headache. Two (3.3%) subjects withdrew because of AEs (bronchoconstriction and fractured rib) during Bronchitol. Two (3.3%) subjects withdrew because of AEs (bronchoconstriction) during placebo. There were no SAEs. There were no deaths. No laboratory data were collected.

Study DPM-B-301

Study DPM-B-301 was a multicentre, randomised, placebo controlled, parallel group, Phase III study of the efficacy and safety of dry powder mannitol in the symptomatic treatment of bronchiectasis. The study was conducted at 22 sites in Australia (15), New Zealand (2) and UK (5). The study included subjects with: diagnosis of non-CF bronchiectasis diagnosed by high resolution CT scan; male or female; aged 15 to 80 years; $FEV_1 \geq 50\%$ predicted and ≥ 1 L; clinically stable for a period of 14 days prior to study entry; daily sputum production of >10 mL on the majority of days in the 3 months prior to enrolment; chronic cough and chronic mucous retention; negative Aridol challenge; and non-smokers. The study treatments were:

1. Spray dried mannitol 320 mg (40 mg x 8 capsules); 12 weeks double blind, 40 weeks open label
2. Non-spray dried mannitol 80 mg (10 mg x 8 capsules); 12 weeks double blind, 52 weeks open label with spray dried mannitol

The efficacy outcome measures were: St Georges Respiratory Questionnaire scores, sputum weight, bronchiectasis symptom scores, Leicester Cough Questionnaire, Incremental Shuttle walk distance, spirometry, gas transfer, airway inflammatory markers, infective episodes and antimicrobial use, pulmonary exacerbations, changes in HRCT scans, functional residual lung volume, airway resistance, and sputum microbiology. The safety outcome measures were: AEs, laboratory safety variables, physical examination.

There were 345 subjects in the safety population, 233 subjects were treated with mannitol and 112 with placebo; 123 subjects commenced open label treatment. A total of 115 subjects were treated with mannitol for 26 weeks, and 99 subjects were treated for 52 weeks. Of the subjects in the ITT population, 224 (65.3%) were female, 119 (34.7%) were male, 334 (97.4%) were Caucasian, 5 (1.5%) were Maori, the age range 18 to 79 years and 297 (86.6%) were smokers. For the ITT analysis, sputum weight decrease in the placebo group relative to mannitol ($p=0.0009$). More subjects in the placebo group than the mannitol commenced antibiotics ($p=0.046$). There were no other significant findings, other than subgroup and per protocol analyses.

In the double blind phase there were 596 AEs reported in 191 (82.0%) subjects in the mannitol group and 294 reported in 90 (80.4%) subjects in the placebo. In the mannitol group the commonest AEs were: lower respiratory tract infection, headache and condition aggravated. In the open label phase there were 753 AEs reported in 117 (95.1%) subjects. The commonest AEs were: lower respiratory tract infection, URTI and condition aggravated.

In the double blind phase there were twelve SAEs reported in ten (4.3%) subjects in the mannitol group and six reported in six (5.4%) subjects in the placebo. Two subjects in the mannitol group died: pneumonia and acute myocardial infarction. In the open label phase there were 31 SAEs reported in 117 (95.1%) subjects.

In the double blind phase 26 (11.2%) subjects in the mannitol group and 3 (2.7%) in placebo discontinued due to AEs. Three subjects in the mannitol group discontinued because of haemoptysis. In the open label phase 7 (5.7%) discontinued due to AEs: atrial fibrillation (1), abdominal distension (1), haematemesis (1), condition aggravated (1), lower respiratory tract infection (1), pneumonia (1) and cough (2).

There were no apparent differences between the treatment groups, or apparent trends over time in mean laboratory parameters or in vital signs.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated.

Pharmacokinetics

Can the sponsor please clarify which studies used the formulation of Bronchitol intended for marketing in Australia?

Efficacy

Can the sponsor please clarify which studies used the formulation of Bronchitol intended for marketing in Australia?

Safety

Has the Sponsor considered the possibility of sponsoring post-marketing studies using CF registries?

Clinical Summary and Conclusions

Clinical Aspects

It was not clear which studies used the formulation of Bronchitol and the dry powder inhaler device intended for marketing in Australia.

The pharmacokinetic studies did not have sufficient sample sizes to enable hypothesis testing. However, the results indicate that mannitol by inhalation has similar bioavailability to oral mannitol, and that there does not appear to be accumulation with multiple dosing.

Benefit Risk Assessment

Benefits

A maximum tolerated dose has not been determined and a plateau in dose effect has not been demonstrated. Hence the sponsor has not demonstrated that the optimal dose has been determined. It appears that the sponsor has determined a dose that worked and then proceeded directly into the pivotal study.

In Study DPM-CF-203 there appeared to be an interaction between mannitol and rhDNase with cancelling of effect in the combined treatment group. This may have been due to the timing of dosing for the two drugs and it may be best to advise separating the dosing by several hours for these two agents.

In Study DPM-CF-301 there was a statistically significant benefit for Bronchitol. An improvement in FEV₁ of around 4% and in FVC of around 3% would also be clinically significant in this patient group. The primary efficacy endpoint was clinically relevant to the indication sought. However, the sponsor clearly had difficulty in deciding on a clinically significant treatment difference when designing the study and the final result indicated a benefit less than originally anticipated in Version 1 of the protocol.

Risks

Overall, Bronchitol had a similar adverse event profile to the control populations. The most commonly reported AEs were those commonly associated with CF such as condition aggravated, cough, and bacteria sputum identified. However, in Study DPM-CF-301, haemoptysis, cough, pharyngolaryngeal pain, toothache, vomiting and diarrhoea occurred more commonly in the mannitol group. Bronchospasm is also a significant AE with Bronchitol, as indicated by the mannitol challenges conducted prior to randomization. In Study DPM-CF-301, haemoptysis was reported as a SAE by 3.4% of subjects in the Bronchitol group. In Study DPM-CF-301, the shift analysis of sputum microbiological findings indicated a slightly higher percentage in the Bronchitol group shifting from no growth to growth. No deaths were reported in any of the studies conducted for the indication of CF. Data from the 6 month open label extension of Study DPM-CF-301 were not included in the submission.

In the studies conducted for the indication of bronchiectasis, the AEs were predominantly those associated with bronchiectasis itself. In Study DPM-B-301 a total of 115 subjects were treated with mannitol for 26 weeks, and 99 subjects were treated for 52 weeks. Two subjects in this study died, but neither death was attributable to Bronchitol.

The sponsor should be encouraged to obtain data for children with CF <6 years. In the absence of such data it is highly likely that there will be significant off-label use of Bronchitol in children <6 years.

Balance

The risk-benefit assessment is in favour of registration of Bronchitol. Although the benefits are clinically significant, they are of a low magnitude. However, the risks of using Bronchitol are minimal according to the data presented in the submission.

Conclusions

Bronchitol should be approved for marketing in Australia for the indication:

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

The sponsor will need to confirm that the formulation of Bronchitol and the dry powder inhaler used in the pivotal study, DPM-CF-301, are identical to those proposed for marketing in Australia.

The sponsor should be required to conduct efficacy and safety studies in children with CF under the age of 6 years.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor provided an EU Risk Management Plan (RMP) which was evaluated by the clinical evaluator. The plan identified that the available data from randomised trials is from 408 subjects treated with mannitol and is sufficient to exclude events with an incidence of 0.9%. It also identified that there are insufficient data in the subpopulations of: elderly >65 years, women of childbearing potential, lactating women, renal and hepatic impairment, cardiac impairment, impaired lung function, genetic polymorphisms, and non-Caucasian subjects. The important identified risks were: haemoptysis; and bronchospasm during and after the initial dose assessment. Cough and pharyngolaryngeal pain are also listed as adverse reactions. No interaction studies have been conducted.

Important missing information identified by the sponsor were:

- Microbial infection via contaminated inhaler
- Cough-related sequelae
- Patients who have had significant haemoptysis in the last 6 months
- Patients requiring home oxygen or needing assisted ventilation
- Children <6 years of age

Off-label use in children <6 years was an identified concern.

The sponsor has proposed routine pharmacovigilance to address these issues.²⁴ However, the clinical evaluator noted that these issues could only be identified by routine pharmacovigilance if there were widespread off-label use. Hence the sponsor will need to design and conduct prospective studies to address these issues.

²⁴ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator noted that the proposed Bronchitol 40 mg capsules are very similar to the registered Aridol 40 mg capsules. Mannitol is a sugar alcohol, an isomer of sorbitol, and is therefore freely soluble in water.

In regard to quality, the evaluator found that "*In vitro* data indicate that Bronchitol may occasionally deliver individually high doses. Pharmaxis attributes this to mannitol accumulating in the device and notes that the total dose from 10 capsules is not affected."

The sponsor claims that patients with baseline FEV₁ < 1L may not be able to achieve the satisfactory inspiratory flow. Repeat inhalations with each capsule can be used to increase the amount of drug delivery to the lungs.

The evaluator requested that the sponsor should include indicative delivered doses, as well as the capsules' content of mannitol, in the Product Information.

Bioavailability

The application included an absolute bioavailability study, Study DPM-PK-101. The study involved use of Aridol, that is, there are small differences in the capsules and more so with the inhaler versus Bronchitol: the mannitol doses were '635 mg' inhaled as Aridol capsules; 500 mg in 50 mL water orally (solution); and 500 mg as a 10% intravenous solution. The inhaler was a "low resistance inhaler" and therefore not directly comparable to the high resistance inhaler intended for Bronchitol.

As might be expected for a sugar alcohol that is not significantly metabolised by humans, mannitol has a significant oral and per inhalation absolute bioavailability: 63% (SD 14) vs 59% (SD 15). The mean urinary excretion over 24 hours was about 55% for the inhalation and oral doses and 87% for the intravenous dose.

Registration was recommended with respect to chemistry and quality control aspects.

Nonclinical

Mannitol for inhalation has been the subject of two previous nonclinical evaluation reports. This submission contained a small amount of new data. Compared to Aridol, Bronchitol is for repeat-daily dosing (not a single cumulative challenge dose) and it has a higher maximum recommended daily dose (800 mg not 635 mg).

Mannitol is extensively metabolised after oral administration (by gut microflora), but little metabolism is observed following IV administration.

It was stated that mannitol has a well known systemic toxicological profile and hence the studies focused on toxicity of mannitol by inhalation after repeat doses.

The evaluator noted a dose-related cough in dogs during and immediately post-dose which is likely to be related to the heavy powder loads being delivered. This generally occurred in the early days (for about 3 weeks) of treatment and reduced as the treatment progressed.

In brief, mannitol has low potential for toxicity in humans at the proposed usage.

The evaluator recommended approval from a nonclinical point of view.

Clinical

Pharmacodynamics

No new data were submitted. The evaluator of the previous (bronchiectasis) submission mentioned that the hyperosmolar effect of mannitol (when inhaled as a powder of respirable particle size) is

thought to be responsible for its mucolytic effect. Two published articles were submitted in this regard. However, the evaluator noted that they were small studies of limited significance (either because of the number of subjects recruited, the multiple endpoints measured or because the indication was different).

Pharmacokinetics

Pharmacokinetic data from Study DPM-PK-101 are shown in Table 2. Study DPM-PK-102 was a study to estimate systemic the pharmacokinetic parameters of inhaled dry powder mannitol, at a dose of 400 mg, in nine subjects with cystic fibrosis. Based on these small numbers, the evaluator commented that “the pharmacokinetic parameters were similar for the two age groups, and for multiple compared with single dosing (see Table 3). There did not appear to be significant accumulation of mannitol with multiple dosing.”

Device Assessment

Study DPM-OSM-403 was of interest because it assessed the capacity of patients to use the high resistance inhaler device (RS01): in brief, patients with cystic fibrosis may need a baseline FEV₁ of >1L to operate effectively the inhaler.

Efficacy

Phase II Studies

There were two dose finding studies (Study DPM-CF-201 and Study DPM-CF-202) and one that explored the therapeutic interaction with rhDNase (Study DPM-CF-203).

Study DPM-CF-201 was a multicentre, double blind, randomised, crossover that was conducted at eight study sites in Australia and New Zealand. It appeared to use 30 mg capsules (dose 420 mg twice daily [bd]) but the high resistance inhaler RS01 was used. A coarse-grained mannitol was used as the inactive comparator. The study showed a statistically significant trend in favour of active treatment - there was a 7% improvement in FEV₁ following Bronchitol and no change following placebo (p=0.008). As explained by the clinical evaluation report, the study was underpowered.

Study DPM-CF-202 was a multicentre, open label, randomised, crossover dose-finding study with no comparator/control arm. Concurrent use of hypertonic saline –and rhDNase - was excluded. The study used multiple phases: Bronchitol for inhalation, initially 400 mg twice daily for two weeks then in random order: 40 mg, 120 mg and 240 mg each for two weeks. The study duration was for 13 weeks in total: four two week administration periods each followed by one week washout periods. The primary efficacy outcome variables were the change between pre and post dose FEV₁ and FVC. A statistically non-significant trend for a dose response was seen, in the opinion of the evaluator. A similar trend was seen for FVC.

Study DPM-CF-203 was an open-label, crossover, three armed study that compared mannitol 400 mg bd vs rhDNase 2.5 mg once daily (od) vs both agents. The primary efficacy outcome measure was the change in FEV₁. Assuming a 15% dropout rate the intended sample size was 48 subjects but a total of 40 subjects were recruited of whom 28 were randomised and 26 received study drug which is less than the intended sample size. The study was underpowered. There were no significant differences between the treatment arms in any of the outcome measures, including the primary endpoint. However, although there appeared to be improvements in FEV₁ in the mannitol and rhDNase alone groups, there was no improvement in the mannitol/rhDNase group.

The Delegate noted that Study 203 does not suggest a role for combined therapy. In fact, all three Phase II studies delivered less than ideal results but studies 201 and 202 lend support to the choice of Bronchitol 400mg bd as the preferred daily dose. Study 203 is an important study for the proposed indication but does not support it.

The Delegate also noted that the evaluator commented that “a maximum tolerated dose has not been determined and a plateau in dose effect has not been demonstrated. Hence the sponsor has not demonstrated that the optimal dose has been determined. It appears that the sponsor has determined a dose that worked and then proceeded directly into the pivotal study.”

“In Study DPM-CF-203 there appeared to be an interaction between mannitol and rhDNase with cancelling of effect in the combined treatment group. This may have been due to the timing of dosing for the two drugs and it may be best to advise separating the dosing by several hours for these two agents.”

Phase III Study

Study DPM-CF-301 was the sole Phase III study and it is the pivotal study of the submission.

The study comprised a double blind phase of 6 months duration followed by an open label phase for 6 months. The latter contributes towards the norm for 12 months of safety data.

The primary efficacy outcome measure was the change from baseline in FEV₁. There were eight secondary endpoints. The sample size calculations estimated 80% power to detect a difference of 70 mL in the change in FEV₁ from baseline with 340 subjects in the ratio 3:2 (mannitol: control) and also that 2/3 of patients would be taking rhDNase. In Version 4 of the protocol, 109 subjects in the mannitol arm and 73 in the control resulted in 80% power to detect a difference of 85 mL.

In fact, 389 subjects were enrolled, 324 subjects were randomised and 295 were included in the ITT population.

The primary efficacy outcome variable favoured mannitol - the mean (95% CI) treatment effect across all time points was 54.17 (24.73 to 83.60) mL, $p < 0.0001$. Other results, as noted by the evaluator, were:

- The overall treatment effect for rhDNase users was 53.82 (14.03 to 93.61) mL, $p = 0.008$.
- The overall treatment effect for rhDNase non-users was 54.54 (10.85 to 98.23) mL, $p = 0.015$.
- These represented a relative improvement in FEV₁ at 26 weeks of 4.11% for the ITT population, 5.11% for rhDNase users and 2.68% for rhDNase non-users.
- The FEV₁ responder analysis indicated benefit in the ITT population and rhDNase users but not in rhDNase non-users (Table 4).
- FVC over time, a secondary end point was more supportive of mannitol.

Overall efficacy conclusions of the evaluator

“In Study DPM-CF-301 there was a statistically significant benefit for Bronchitol. An improvement in FEV₁ of around 4% and in FVC of around 3% would also be clinically significant in this patient group. The sponsor clearly had difficulty in deciding on a clinically significant treatment difference when designing the study and the final result indicated a benefit less than originally anticipated in Version 1 of the study protocol.”

Safety

The evaluator of the previous bronchiectasis studies mentioned that the adverse event patterns were well established; there were cough, bronchospasm and pharyngeal pain more commonly reported with mannitol than placebo.

In this submission, Study 301 provided the largest and longest exposure in cystic fibrosis: a total of 112 (58.3%) subjects was exposed to mannitol for 26 weeks; a total of 63 subjects aged 6-17 years was exposed to mannitol for a mean (SD) duration of 140.9 (66.62) days. A total of 822 adverse events were reported in 154 (87.0%) subjects in the mannitol group and 541 AEs in 109 (92.4%) subjects in the control.

Haemoptysis, cough, pharyngolaryngeal pain, toothache, vomiting and diarrhoea occurred more commonly in the mannitol group (Table 5). Haemoptysis was more commonly reported as a serious adverse event in the mannitol group, six (3.4%) subjects compared with two (1.7%) in the control.

Deaths did not occur in any of the cystic fibrosis studies.

As noted by the evaluator: “In Study DPM-CF-301, 28 (15.8%) subjects in the mannitol group and 10 (8.5%) in the control withdrew because of an AE. The most frequently reported AEs leading to discontinuation were: cough, condition aggravated and haemoptysis. Haemoptysis lead to five subjects discontinuing in the mannitol group and none in the control.”

Risk Management Plan

The Risk Management Plan proposes only routine pharmacovigilance. The evaluator suggested that the sponsor should investigate the possibility of sponsoring studies using cystic fibrosis registries in order to identify serious adverse events during the use of Bronchitol.

As for further studies, the evaluator requested that “the Sponsor should be encouraged to obtain data for children with CF <6 years. In the absence of such data it is highly likely that there will be significant off-label use of Bronchitol in children <6 years.”

Risk-Benefit Analysis

Delegate Considerations

The applicant should confirm that “rhDNase” means quite specifically dornase alfa and that its use was consistent by way of dose and administration with the approved Australian product information or disclose how it was not. The approved product information of dornase alfa suggests a significant treatment effect for dornase alfa alone.

As hypertonic saline is the widely used hyperosmotic agent, it would therefore have been an appropriate active comparator in clinical trials. This may have to be pursued.

The pivotal study may marginally satisfy the requirements for the submission of one pivotal study as stipulated in the TGA-approved EU Guidelines.²⁵ The evidence is certainly not “exceptionally compelling”; especially in relation to external validity, the study outcome does not establish that mannitol relieves the symptoms affecting quality of life or most other secondary endpoints nor has its role against hypertonic saline been explored

Overall, there is modest efficacy data to recommend approval and the Delegate was inclined to approve this application conditionally upon commitment to further studies. The added value of mannitol in addition to dornase alfa seems small. Ultimately, the worth of exposing patients with cystic fibrosis to an agent such as mannitol that is associated with numerous common adverse effects relates to long term improved morbidity and mortality or at least improved quality of life to offset the commonly experienced adverse reactions.

The Delegate asked the following questions of the Advisory Committee.

1. Is the dose finding adequate?
2. Are the results for the primary efficacy variable in the Phase III study persuasive, that is, are they clinically significant? As this is a one-study submission, the relevant guideline would suggest that both statistical and clinical significance is necessary.
3. Is the pivotal study transferrable to typical outpatient care settings?

²⁵ EMEA, Committee for Proprietary Medicinal Products (CPMP), 31 May 2001. Points to Consider on Application with 1. Meta-analyses, 2. One Pivotal Study, CPMP/EWP/2330/99.

4. Is there any need to conduct further postmarketing studies? If so, what endpoints should be tested?

5. Given the nature of the device that is proposed for use, is a study in children aged under 7 years necessary?

The Delegate proposed to approve the submission for the following indication:

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

As a condition of registration, the sponsor should commit to post-marketing data capture, desirably via a clinical trial, to demonstrate the long term efficacy and safety of Bronchitol in cystic fibrosis.

Response from Sponsor

In its pre-ACPM response, the sponsor addressed the questions raised by the Delegate.

Pulmozyme

For the purpose of this application the terms rhDNase, dornase alfa and Pulmozyme were used to refer to the same drug. It was, however, acknowledged that dornase alfa is the Australian Approved Name (AAN) for this drug.

In the pivotal clinical trial, dornase alfa was considered to be a concomitant medication and was used at the treating physician's discretion. The current approved dose is nebulised inhalation of 2.5 mg once daily. Concomitant medication, including dornase alfa, was recorded as part of each patient's medical history. "Users" were defined as those subjects who stated at screening that they routinely used dornase alfa. Subjects who stated at screening that they did not use dornase alfa routinely were defined as "non users".

Hypertonic Saline

Hypertonic saline (HS) for inhalation as a hyperosmotic agent is not considered an appropriate comparator in clinical trials in CF for a number of reasons. Inhaled HS has not been evaluated or approved for therapeutic use in CF by any regulatory agency in the world. The appropriate dosage and administration has not been established or standardised, making it difficult to use as a comparator. The sponsor discussed the reasons why HS is not a suitable for use as a comparator in clinical trials in pulmonary CF.

Dose Finding

The Phase II study (DPM-CF-202) investigated dose response in 48 CF patients. Four doses were trialled: 40 mg, 120 mg, 240 mg and 400 mg bd. The 40 mg dose showed no efficacy at all. The 120 mg, 240 mg and 400 mg doses all showed increasing improvement in FEV₁ and FVC. The change in FEV₁ was significantly greater on 400 mg compared to 40 mg but not to 120 or 240 mg.

However the changes in FVC were significantly greater at 400 mg than all the other doses. The 400 mg dose therefore demonstrated greater improvements in both FEV₁ and FVC than lower doses and as this was the primary outcome it was determined that the 400 mg dose was the most efficacious.

Although the highest possible dose has not been formally established, the use of more than 10 mannitol capsules for each dose may compromise compliance. It is necessary to consider the practical and physical limitations of the dosage form. Each increase in dose involves an increase in the number of capsules a patient is required to take (40 mg = 1 capsule, 120 mg = 3 capsules, 240 mg = 6 capsules, 400 mg = 10 capsules). This presents a compliance issue which must be a key consideration in a patient population with an already high treatment burden. The 400 mg dose bd is

a reasonable balance between acceptability and efficacy. It is well tolerated, with sufficient compliance to achieve a measurable, clinically meaningful benefit.

Clinical Significance

The measure of absolute change in FEV₁ remains a gold standard in CF assessment and is a recognized primary variable in EU guidelines. Decreases in FEV₁ are associated with increased morbidity and mortality. A supportive measure for improvement in FEV₁ is change in pulmonary exacerbation rates. These are also associated with increased morbidity and mortality, and correlated with changes in FEV₁. Other measures of lung function, including FVC, FEF₂₅₋₇₅ and PEF, provide supportive data.

The current rate of decline in FEV₁ of CF patients has been estimated as low as 0.65% per year (Que et al, 2006).²⁶ In the pivotal clinical trial (DPM-CF-301) patients treated with Bronchitol had a sustained average improvement in FEV₁ of 6.5%. Such an improvement may potentially represent a 10 year benefit in survival, a significant benefit when considering the average life expectancy is not more than 30 years. Whether or not Bronchitol can eventually be seen to be truly disease modifying should not detract from the incremental benefit it can contribute, thereby delaying the time to lung failure and the need for a transplant or in the time to death.

The number of acute pulmonary exacerbations per year is an important surrogate for prediction of death in CF. Recent data has shown the FEV₁ of patients who have an acute pulmonary exacerbation does not return to the pre-exacerbation value, and hence each exacerbation leads to long term increased morbidity (Sanders et al, 2010).²⁷ Moreover, the medical costs and patient medical burden is dramatically reduced with a decrease in acute pulmonary exacerbations. The proportion of patients with at least one PDPE was reduced by 35.4% (28.1% control vs 18% Bronchitol) which is considered clinically important and comparable to reductions seen with dornase alfa.

The improvement in FEV₁ in patients treated with Bronchitol in the pivotal clinical trial was 6.5% which is comparable to the improvement of 5.8% achieved in the dornase alfa clinical trial (Fuchs et al, 1994).²⁸ The benefit of Bronchitol compared to dornase alfa should be considered in the historical context such that the standard of care was lower when the dornase alfa study was conducted. Bronchitol has demonstrated a similar size of benefit even on top of regular dornase alfa therapy and other advances in standard of care such as inhaled antibiotics, azithromycin, etc.

Further, the clinically significant reduction in incidence of exacerbations in the Bronchitol study is comparable to reductions noted with dornase alfa.

In summary, the improvement in lung function with the use of Bronchitol is both statistically and clinically significant. This significance translates to clinical relevance via the reduction in exacerbations which contribute to the decline in lung function, the main source of morbidity in CF.

The improvements seen in patients treated with Bronchitol are equivalent and additional to the current standard of care which includes dornase alfa therapy.

²⁶ Que C, Cullinan P, Geddes D. Improving rate of decline of FEV₁ in young adults with cystic fibrosis. *Thorax* 2006; 61: 155-157.

²⁷ Sanders DB, Hoffman LR, Emerson J et al. Return of FEV₁ after pulmonary exacerbation in children with cystic fibrosis. *Pediatr Pulmonol* 2010; 45: 127-134.

²⁸ Fuchs HJ, Borowitz DS, Christiansen DH et al. Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. *N Engl J Med* 1994; 331: 637-642.

Transferrable to Typical Patient

The patient population studied was representative of the wider CF patient population. The age range was from 6 to 56 years, with the children and adolescents well represented (17.5 % and 18.1 % of mannitol ITT). The disease severity, FEV₁ % predicted, ranged from 26% to 93% (median 62.6% in the mannitol ITT). The use of dornase alfa was evenly divided in the mannitol group (96 users vs 81 non-users in mannitol ITT). The pivotal clinical trial is directly transferrable to the typical out-patient care setting. There was no change to the standard of care patients received during the study; physiotherapy and exercise routines, and routine medications were maintained (other than exclusion of HS). Clinic visit frequency in the study (at Weeks 0, 6, 14 and 26) was representative of usual out-patient visits to CF clinics as part of ongoing maintenance care. In the open-label extension the visits were less frequently required (at Weeks 38, 52, 62 and 76).

The proposed Bronchitol treatment protocol requires medical supervision of the initiation dose, to exclude bronchial hyperresponsiveness, followed by chronic therapy requiring no more than the typical out-patient clinic care.

Postmarketing Studies

This application presented the double blind phase (26 weeks) of the pivotal study DPM-CF-301. The open label extensions have been completed, providing a total of 12 months efficacy data demonstrating maintained efficacy, and a total of 18 months safety data confirming the acceptable safety profile.

A second, confirmatory pivotal study is near completion of the open-label phase. This study (DPMCF-302) is essentially the same as the first; a multi-centre, randomized, double-blind, placebo-controlled, parallel-group trial enrolling 300 CF patients for 26 weeks with 6 month open label extension.

The sponsor considered these data sufficient to demonstrate the safety and efficacy of Bronchitol in CF, and there is no intention to conduct further studies. There would be no objection to submission of the DPM-CF-301 open label extension, and the DPM-CF-302 confirmatory pivotal study for evaluation, when available, if required to satisfy a condition of registration.

Paediatric Studies

It is not possible to investigate Bronchitol for use in children under 6 years of age, because they are not capable of performing reliable, repeatable spirometry (Australia National Asthma Council – Asthma Management Handbook 2006, British Thoracic Society Guideline for Management of Asthma 2008, American Thoracic Society 2005).

The clinical investigation of Bronchitol requires a patient to perform reliable, repeatable spirometry in order to measure their lung function. Inability to do so gives rise to two main issues:

- Safety - reliable spirometry data is needed for the mannitol tolerance test which confirms the absence of bronchial hyperresponsiveness and safety of the patient to receive treatment. Without this test it would not be possible to confirm the safety of Bronchitol use in a patient.
- Efficacy - reliable spirometry data is a necessary measure of lung function (FEV₁, FVC, etc), without which it is not possible to determine the efficacy of the treatment.

The European Medicines Agency has granted a waiver for children less than 6 years of age in the Paediatric Investigation Program (PIP) for Bronchitol in CF, on the grounds that clinical studies are not feasible. The sponsor does not intend to investigate the use of Bronchitol in children less than 6 years of age.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following indication:

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

In making this recommendation, the ACPM considered the overall risk benefit to be positive; however, the ACPM expressed concern that the maximum dose 400 mg was not clearly evidenced by the design of the study.

Specific conditions of registration should include:

- A commitment by the sponsor to conduct both clinical trials and post-marketing data capture to demonstrate the long term efficacy and safety of this product in cystic fibrosis.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the application for registration of a new dose, extension of indication and additional trade name for Bronchitol containing mannitol 40 mg powder for inhalation hard capsule, indicated for:

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

A specific condition of registration was that:

- Information from both clinical trials and post-marketing data that demonstrates the long term efficacy and safety of this product in cystic fibrosis is to be forwarded to the TGA as soon as it becomes available.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

BRONCHITOL

Mannitol powder for inhalation

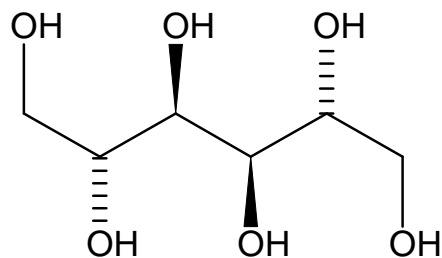
Name of the Medicine

Mannitol. Also known as D-mannitol.

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

CAS number: 69-65-8.

Structural Formula:



Description

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

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

Pharmacology

Pharmacodynamics

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

Pharmacokinetics

Absorption:

In a study of 18 healthy male adult volunteers, using an Aridol inhaler, the absolute bioavailability of mannitol powder for inhalation by comparison to mannitol administered intravenously was 0.59 ± 0.15 .

The rate and extent of absorption of mannitol after inhaled administration was very similar to that observed after oral administration. The T_{max} after inhaled administration was 1.5 ± 0.5 hours.

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

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

Metabolism:

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

Distribution:

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

Elimination:

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

Clinical Trials

Study DPM-CF-301 was a Phase 3, double blind, randomised, parallel arm, controlled, intervention study that was of 6 months duration, followed by an open label phase for 6 months. The primary efficacy outcome measure was the change from baseline in FEV₁. There were eight secondary endpoints. The study treatments during the double blind phase were:

1. Mannitol, 40 mg, 10 x 40 mg capsules twice daily, or
2. Mannitol for inhalation at a sub-therapeutic dose (control), 10 x 5 mg capsules twice daily.

During the open label phase all subjects received mannitol 400 mg twice daily.

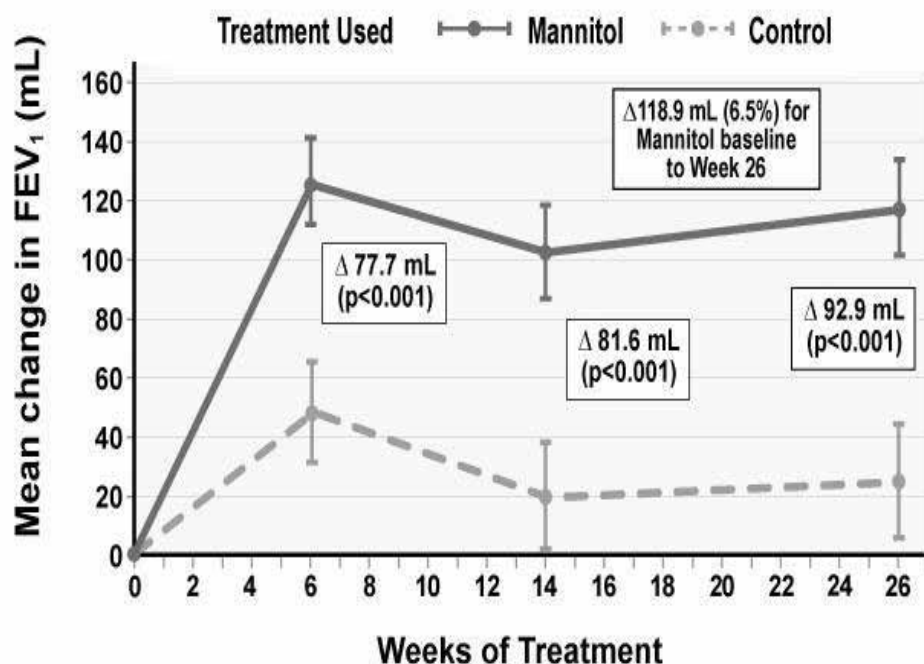
Treatments were administered by dry powder inhaler, with a 5 second breath hold post inhalation after each capsule. Treatments were preceded by salbutamol 400 µg. Physiotherapy followed study treatment and preceded dornase alfa. Completion to 26 weeks was slightly higher in the control group: 198 (61.1%) randomised subjects completed the 26 week double blind treatment phase, including 112 (58.3%) in the mannitol group and 86 (65.2%) in the control group.

In the ITT population (n=295), at week 26 the change from baseline in FEV₁ was 118.9 mL (95%CI, 85.6 to 152.2) compared to 26 mL (95% CI, -11.6 to 63.6) on control treatment, Δ 92.9 mL, $p < 0.001$. The relative mean change from baseline in FEV₁ was 6.5 % (95% CI, 4.72 to 8.3) compared to 2.39 % (95% CI, 0.37 to 4.41) on control treatment, Δ 4.11%. Improvement in FEV₁ with inhaled mannitol was evident by week 6 compared to control and remained significant at weeks 14 and 26 (77.7, 81.6 and 92.9 mL respectively).

In dornase alfa users, at week 26, the change from baseline in FEV₁ was 81.03 mL (95% CI, 35.49 to 126.56) compared to -27.78 mL (95% CI, -78.17 to 22.61) on control treatment, Δ 108.81 mL, $p = 0.002$. Improvement in FEV₁ with inhaled mannitol was evident by week 6 compared to control and remained significant at weeks 14 and 26 (63.3, 75.8 and 108.8 mL respectively).

In dornase alfa non-users, at week 26, the change from baseline in FEV₁ was 158.31 mL (95% CI, 110.08 to 206.54) compared to 88.7 mL (95% CI, 32.12 to 145.27) on control treatment, Δ 69.61 mL, $p = 0.064$. Improvement in FEV₁ with inhaled mannitol was evident by week 6 compared to control and remained significant at week 14 but not at week 26 (95.3, 89.7, 69.6 mL respectively).

Figure 1: Change in FEV₁ by timepoint in the ITT population*



*Mean change in FEV₁ is calculated as least square means (\pm SE) adjusted for treatment group age, week of study, dornase alfa use, baseline FEV₁, sex, baseline FEV₁ % predicted, region and treatment week.

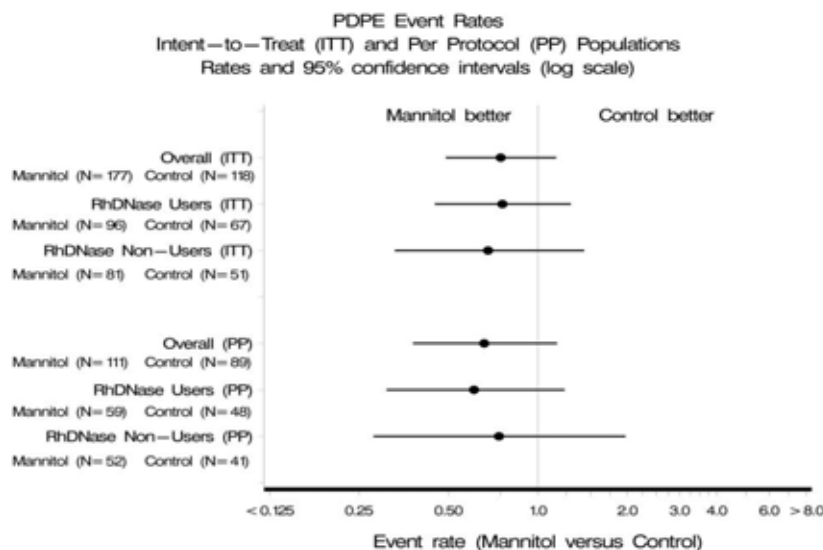
The mean FVC improvement was 70.89 mL (95% CI, 29.9 to 111.88) greater for subjects treated with mannitol compared to subjects treated with control, $p < 0.001$. At week 26, the absolute change from baseline in FVC was 128.9 mL (95% CI, 81.9 to 175.8) compared to 15.9 mL (95% CI, -37.2 to 68.9) on control treatment (Δ 113 mL, $p = 0.002$). The relative mean change from baseline in FVC was 4.95% (95% CI, 3.2 to 6.7) compared to 1.5% (95% CI, -0.4 to 3.5) on control treatment (Δ 3.4%, $p = 0.009$).

Trends in favour of Bronchitol for the absolute change from baseline in FEV₁/FVC and FEF₂₅₋₇₅ were not found to be significantly different to the control. Absolute change from baseline in PEF was significantly increased on mannitol treatment by a meaningful 236.6 mL/s, and represented a 5.7% increase from baseline at 26 weeks.

The rates of pulmonary exacerbations (PE) and protocol defined pulmonary exacerbations (PDPE) were both less common in the mannitol group than in the control group. There was a reduction in the incidence of PDPE of 35.4% (mannitol 18.1%; control 28.0%), and a reduction in the incidence of PE of 27.8% (mannitol 36.7%; control 50.8%). The trends seen in time to first exacerbation being

increased on mannitol treatment are significant in the PP population for both PDPE and PE (P=0.026 and 0.025). This trend is irrespective of concomitant dornase alfa use.

Figure 2: PDPE Event Rates (log scale)



Quality of Life measures showed differences in the physical, vitality and respiratory domains that were not statistically significant between active and control groups.

A phase 2 study (DPM-CF-202) investigated dose response in 48 CF patients; 19 adults and 29 children (7-68 years, median 15.0 years). The primary efficacy outcome variables were the change between pre and post dose FEV₁ and FVC. Four doses were trialed: 40 mg, 120 mg, 240 mg, and 400 mg b.i.d. The 40 mg dose showed no efficacy. The 120 mg, 240 mg and 400 mg doses all showed increasing improvement in FEV₁ and FVC. The trend was not statistically significant. The change in FEV₁ was significantly greater on 400 mg compared to 40 mg but not to 120 or 240 mg. However the changes in FVC were significantly greater at 400 mg than all the other doses. The 400 mg dose therefore demonstrated greater improvements in both FEV₁ and FVC than lower doses and as this was the primary outcome it was determined that the 400 mg dose was the most efficacious, irrespective of age group. No higher dose has been tested.

Indications

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

Contraindications

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

Precautions

Asthma:

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 to their physician.

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 hyperresponsive, they should not be prescribed the therapeutic dose regimen of Bronchitol. The usual precautions regarding bronchial hyperresponsiveness monitoring apply.

Bronchitol may cause bronchoconstriction requiring treatment, even in patients who were not hyperresponsive to the initiation dose of inhaled mannitol.

Impaired Lung Function:

Safety and efficacy have not yet been demonstrated in patients with a FEV₁ of less than 30% of predicted.

Impaired Hepatic / Renal Function

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

Haemoptysis:

Patients with a previous history of significant episodes of haemoptysis (>60 mL) should be carefully monitored. Bronchitol has not formally been studied in patients with a history of haemoptysis in the previous 6 months. Please refer to the Adverse Effects section.

Effects on Fertility

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

Use in Pregnancy (Pregnancy Category B2)

For mannitol no clinical data on exposed pregnancies are available. Animal reproduction studies have not been carried out with inhaled mannitol. However, studies with orally administered mannitol indicate no teratogenic effects in mice or rats at daily doses up to 1.6g/kg, or in hamsters at 1.2g/kg/day.

As the effects of a possible hyperresponsiveness reaction on the mother and/or the fetus are unknown, caution should be exercised when prescribing Bronchitol to pregnant women.

Use in Lactation

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

Paediatric use

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

Use in the Elderly

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

Carcinogenicity

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

Genotoxicity

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

Interactions

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

Effects on Laboratory tests

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

Adverse Effects

In study DPM-CF-301, subjects in the mannitol group used the study medication from 1 to 218 days with a mean (SD) exposure of 135.5 (70.09) days. Exposure in the adolescent and paediatric subgroups was 145.7 (64.58) and 136.2 (69.24) days respectively.

A total of 822 adverse events (AE) were reported in 154 (87.0%) subjects in the mannitol group and 541 AE in 109 (92.4%) subjects in the control group. Treatment related AE were reported by 72 (40.7%) subjects in the mannitol group compared to 26 (22.0%) subjects in the control group. Haemoptysis, cough, pharyngolaryngeal pain, toothache, vomiting and diarrhoea occurred more commonly in the mannitol group.

In Study DPM-CF-301, 28 (15.8%) subjects in the mannitol group and 10 (8.5%) in the control withdrew because of an AE. The most frequently reported AEs leading to discontinuation were: cough, condition aggravated and haemoptysis.

Table 1 : Most Commonly Reported Treatment-Emergent Adverse Events by MedDRA Preferred Term $\geq 2.0\%$ in Any Treatment Group During the Blinded Study Period.

Preferred Term	Mannitol [N=177] n (%)	Control [N=118] n (%)
Condition aggravated	57 (32.2)	42 (35.6)
Cough	45 (25.4)	24 (20.3)
Headache	38 (21.5)	28 (23.7)
Bacteria sputum identified	33 (18.6)	22 (18.6)
Nasopharyngitis	25 (14.1)	17 (14.4)
Lower respiratory tract infection	15 (8.5)	20 (16.9)
Haemoptysis	21 (11.9)	10 (8.5)
Pharyngolaryngeal pain	24 (13.6)	5 (4.2)
Upper respiratory tract infection	14 (7.9)	8 (6.8)
Abdominal pain upper	12 (6.8)	7 (5.9)
Arthralgia	12 (6.8)	7 (5.9)
Productive cough	12 (6.8)	7 (5.9)
Vomiting	13 (7.3)	4 (3.4)
Back pain	7 (4.0)	7 (5.9)
Abdominal pain	6 (3.4)	8 (6.8)
Toothache	9 (5.1)	3 (2.5)
Constipation	6 (3.4)	5 (4.2)
Diarrhoea	9 (5.1)	1 (0.8)
Pyrexia	7 (4.0)	2 (1.7)
Fungus sputum test positive	6 (3.4)	3 (2.5)
Ear pain	5 (2.8)	4 (3.4)
Nausea	4 (2.3)	5 (4.2)
Chest discomfort	6 (3.4)	2 (1.7)
Tonsillitis	6 (3.4)	2 (1.7)
Fatigue	5 (2.8)	3 (2.5)
Nasal congestion	4 (2.3)	4 (3.4)
Wheezing	4 (2.3)	4 (3.4)
Epistaxis	5 (2.8)	2 (1.7)
Musculoskeletal chest pain	5 (2.8)	2 (1.7)
Rash	4 (2.3)	3 (2.5)
Viral infection	3 (1.7)	3 (2.5)
Malaise	3 (1.7)	3 (2.5)
Oral candidiasis	4 (2.3)	2 (1.7)
Pain in extremity	4 (2.3)	2 (1.7)
Rhinorrhoea	4 (2.3)	2 (1.7)
Asthma	2 (1.1)	3 (2.5)
Influenza like illness	4 (2.3)	1 (0.8)
Insomnia	4 (2.3)	1 (0.8)
Musculoskeletal pain	4 (2.3)	1 (0.8)
Sinus headache	4 (2.3)	1 (0.8)
Chest pain	1 (0.6)	3 (2.5)
Stomach discomfort	1 (0.6)	3 (2.5)
Viral upper respiratory tract infection	0 (0.0)	4 (3.4)
Rhinitis allergic	0 (0.0)	3 (2.5)

Initiation Dose Assessment:

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

Table 2 contains only the adverse reactions for which a causal relationship with medicinal product treatment could reasonably be established. Frequencies given are based on the observations on the day of screening prior to commencement of the pivotal comparative clinical study investigating the effect of Bronchitol as an add-on to current therapy in cystic fibrosis patients.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Frequency of adverse reactions with Bronchitol on the day of screening

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

Therapeutic Dose Regimen:

Most patients taking Bronchitol can be expected to experience adverse reactions. The most commonly observed adverse reaction associated with the use of Bronchitol is cough. The clinically most important adverse reaction associated with the use of Bronchitol is haemoptysis.

Table 3 contains only the adverse reactions for which a causal relationship with medicinal product treatment could reasonably be established. Frequencies given are based on the observations during a pivotal comparative clinical study investigating the effect of Bronchitol as an add-on to current therapy in cystic fibrosis patients.

Frequencies are defined as described for Table 2.

Table 3: Frequency of adverse reactions with Bronchitol during the treatment phase

System Organ Class	Very Common	Common	Uncommon
Infections and infestations			Oral candidiasis* Staphylococcal infection
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders		Headache	Dizziness
Ear and labyrinth disorders			Ear Pain
Respiratory, thoracic and mediastinal disorders	Cough	Haemoptysis Bronchospasm Wheezing* Asthma* Condition aggravated Pharyngolaryngeal pain Productive cough Chest discomfort Bacteria sputum identified*	Fungus sputum test positive Respiratory tract congestion Throat irritation* Rhinorrhoea
Gastrointestinal disorders		Vomiting Post-tussive vomiting	Gastrooesophageal reflux disease Glossodynia
Skin and subcutaneous tissue disorders			Acne Pruritus Rash Cold sweat
Musculoskeletal and connective tissue disorders			Arthralgia Joint stiffness Musculoskeletal chest pain
Renal and urinary disorders			Urinary incontinence
General disorders and administration site conditions			Hernia pain Fatigue

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

Haemoptysis:

Haemoptysis led to 5 subjects discontinuing in the mannitol group and none in the control. Haemoptysis was more commonly reported as a serious adverse event in the mannitol group, 6 (3.4%) subjects compared with 2 (1.7%) in the control. However, the proportion of patients who experienced haemoptysis as an AE or during exacerbation was 15.8% in the mannitol arm and 15.3% in the control arm.

Cough:

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

Dosage and Administration

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

Initiation Dose Assessment:

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

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

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

- Step 1: Patients baseline 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.

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

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

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

- $\geq 10\%$ fall in SpO₂ at any point of the assessment
- FEV₁ fall is $\geq 20\%$ at 240 mg cumulative dose
- FEV₁ has fallen $\geq 20\%$ (from baseline) at the end of the assessment and does not return to within $<20\%$ of baseline, within 15 minutes.

Therapeutic Dose Regimen:

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

The recommended dosage of Bronchitol is 400 mg twice a day.

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

The inhaler device is to be replaced after one week of use. If the inhaler does require cleaning, ensure the device is empty then wash in warm water and before re-use, allow the inhaler to thoroughly air dry.

A bronchodilator must be administered 5-15 minutes before Bronchitol is used. The recommended order of treatment is: bronchodilator, Bronchitol, physiotherapy / exercise, then dornase alfa (if applicable).

Overdosage

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

Presentation and Storage Conditions

Bronchitol 40 mg capsules are presented in double aluminium blisters in cartons containing 10, 140 or 280 capsules for initial dose and chronic use respectively. The capsules are clear and imprinted with "PXS 40 mg".

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

The 7 day carton contains 14 blister strips (of 10 capsules each) and one inhaler device.

The 14 day carton contains 28 blister strips (of 10 capsules each) and two inhaler devices.

Store below 25°C.

Name and Address of the Sponsor

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Poison Schedule of the Medicine

Mannitol is Unscheduled.

Date of Approval

07 February 2011.