

6.12 MANNITOL capsule containing powder for inhalation, 40mg, Bronchitol[®], Pharmaxis

1 Purpose of Application

- 1.1 The minor submission sought to amend the PBS listing for dry powder inhaler (DPI) mannitol to reduce the complexity of the current restriction and to permit the combination use of DPI mannitol with dornase alfa.

2 Requested listing

- 2.1 The submission sought the following deletions to the existing listing (*in strikethrough text*):

Name, Restriction, Manner of administration and form	Max. Qty packs	No. of Rpts	DPMQ	Proprietary Name and Manufacturer
MANNITOL Pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers, 1	4	5	\$ [REDACTED] (Private) \$ [REDACTED] (Public)	Bronchitol [®] Pharmaxis

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic fibrosis
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (Private hospital) <input checked="" type="checkbox"/> Streamlined (Public hospital)
Clinical criteria:	<p>Patient must have been assessed for bronchial hyperresponsiveness as per the TGA approved Product Information mannitol initiation dose assessment, prior to mannitol therapy. If the patient has a negative hyperresponsiveness test they may be eligible for PBS subsidised treatment with mannitol,</p> <p>AND</p> <p>Patient must have a forced expiratory volume in 1 second (FEV1) greater than 30% predicted for age, gender and height,</p> <p>AND</p> <p>Patient must be intolerant or inadequately responsive to dornase alfa,</p> <p>AND</p> <p>Patient must have evidence of chronic suppurative lung disease (cough and sputum most days of the week, or greater than 3 respiratory tract infections of more than 2 weeks' duration in any 12 months, or objective evidence of obstructive airways disease).</p>
Population criteria:	<p>Patient must be 6 years of age or older.</p> <p>Patient must be assessed at a cystic fibrosis clinic/centre which is under the control</p>

	<p>of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis. The prescribing of mannitol therapy under the HSD program is limited to such physicians. If attendance at such a unit is not possible because of geographical isolation, management (including prescribing) may be by a specialist physician or paediatrician in consultation with such a unit.</p> <p>The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at an established lung function testing laboratory, unless this is not possible because of geographical isolation.</p> <p>Prior to mannitol therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease.</p> <p>Initial therapy is limited to 3 months treatment with mannitol at a dose of 400 mg twice daily.</p> <p>FEV1 measurement (single test under conditions as above) and a global assessment of the patient involving the patient, the patient's family (in the case of paediatric patients), the treating physician(s) and an additional independent member of the cystic fibrosis treatment team must be undertaken and documented following 3 months of initial therapy.</p> <p>To be eligible for continued PBS-subsidised treatment with mannitol following 3 months of initial treatment:</p> <p>(1) the patient must demonstrate no deterioration in FEV1 compared to baseline; AND</p> <p>(2) the patient or the patient's family (in the case of paediatric patients) must report improvement in the patient's airway clearance; AND</p> <p>(3) the treating physician(s) must report a benefit in the clinical status of the patient.</p> <p>Further reassessments involving the patient, the patient's family (in the case of paediatric patients), the treating physician(s) and an additional independent member of the cystic fibrosis treatment team must be undertaken and documented at six-monthly intervals to establish that all agree that mannitol treatment is continuing to produce worthwhile benefits. Mannitol therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.</p> <p>Other aspects of treatment, such as physiotherapy, must be continued.</p> <p>Where there is documented evidence that a patient already receiving mannitol therapy would have met the criteria for subsidy then the patient is eligible to continue treatment under the HSD program. Where such evidence is not available, patients will need to satisfy the initiation and continuation criteria as for new patients. (Four weeks is considered a suitable wash-out period.)</p>
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Clinical criteria:	<p>Patient must have initiated treatment with mannitol prior to 1 August 2012,</p> <p>AND</p> <p>Patient must have undergone a comprehensive assessment involving the patient's family, the treating physician and an additional independent member of the cystic fibrosis team, which documents agreement that mannitol treatment is continuing to produce a worthwhile benefit.</p>
Population criteria:	<p>Patient must be 6 years of age or older.</p> <p>Further reassessments are to be undertaken and documented every 6 months. Treatment with mannitol should cease if there is not agreement of benefit as there is always the possibility of harm from unnecessary use.</p>
Prescriber Instructions	<p>Note It is highly desirable that all patients be included in the national cystic fibrosis patient database.</p> <p>Note Mannitol is not PBS-subsidised for use in combination with PBS-subsidised dornase alfa.</p>

Secretariat comments

- 2.2 The submission stated that the proposed changes have the full support of the Cystic Fibrosis Australia Centre Directors and the Cystic Fibrosis Special Interest Group of the Thoracic Society of Australia and New Zealand (TSANZ).
- 2.3 The submission requested removal of the criterion limiting treatment to patients with FEV₁ greater than 30% of predicted for age, gender and height. The submission argued that this criterion is redundant as the current TGA-approved product information already warns against using DPI mannitol in patients with severely impaired lung function (FEV₁ < 30%) due to a lack of clinical data. The Pre-PBAC Response stated that the sponsor supports the recommendations regarding restriction wording outlined by TSANZ, wherein the FEV₁ criterion is retained within a simplified listing.
- 2.4 The submission requested removal of the criterion limiting treatment to patients who are intolerant or inadequately responsive to dornase alfa on the basis that this requirement is redundant as it is already specified in the TGA approved indication. The removal of this criterion would potentially allow subsidised treatment for an off-label use. The pivotal clinical trials included a broader population of patients than the current PBS restriction as they enrolled patients with no prior exposure to dornase alfa, patients who were intolerant or inadequately responsive to dornase alfa and patients who were currently using dornase alfa. The sponsor previously presented subgroup data to the PBAC for patients intolerant or inadequately responsive to dornase alfa and patients who were currently using dornase alfa but did not present any data on DPI mannitol use in the subgroup of patients with no prior exposure to dornase alfa. The Pre-PBAC response argued that there is no mechanistic basis to suggest that efficacy and/or safety would be compromised in the small sub-group of otherwise eligible patients who have had no prior exposure to dornase alfa.

- 2.5 The submission requested removal of the criterion limiting treatment to patients with specific disease symptoms (chronic suppurative lung disease, respiratory tract infection, obstructive airways disease) as it is not consistent with the sponsor's understanding of the way cystic fibrosis (CF) is treated in Australia. The pivotal trials for DPI mannitol did not use the presence/absence of respiratory complications as eligibility criteria. This criterion appeared to have originated from the dornase alfa PBS restriction which is TGA-approved and PBS-listed for the chronic treatment of respiratory complications associated with CF.
- 2.6 The submission requested removal of the criterion limiting treatment to adults and children 6 years of age and older on the basis that this requirement is redundant as it is already specified in the TGA approved indication. There was no clinical evidence to support the use of DPI mannitol in children less than 6 years of age. In contrast, dornase alfa has been assessed in younger children and is both TGA-approved and PBS-listed for this patient group. The Pre-PBAC Response argued that the intention of removing this criterion was not to remove the restriction on use in children under 6 years, but to simplify the restriction by removing elements that are covered in the approved indication.
- 2.7 The submission requested removal of the criterion requiring lung function testing to be conducted by an independent doctor for simplification purposes.
- 2.8 The submission requested removal of the 'grandfathering' provision as it was no longer necessary given DPI mannitol has been listed on the PBS for over 2 years and patients are unlikely to receive treatment under this provision.
- 2.9 The submission requested removal of the criterion preventing combination treatment with DPI mannitol and dornase alfa due to physician confusion about what constitutes combination therapy (e.g. patients cycling between DPI mannitol/dornase alfa treatment courses, patients alternating treatments in morning/evening, patients alternating treatments on weekdays/weekends, patients intensifying treatment during exacerbations, etc). The submission claimed that given the different mechanisms of action between the two therapies it was likely that various combinations of the two agents would be beneficial to patients. The Pre-PBAC Response noted that the TSANZ submission provided support for the co-administration or sequential use of inhaled mannitol and dornase alfa, as the use of multiple therapies in combination or sequentially to enhance mucus clearance in CF patients represents best practice. The Pre-PBAC Response also argued that previously submitted data (see paragraph 4.8) supported the clinical benefit of DPI mannitol either alone or with dornase alfa.
- 2.10 The submission noted that the PBS listing for DPI mannitol was originally modelled on the PBS listing for dornase alfa. However, the submission argued that there was no specific reason why the listing of DPI mannitol should reflect dornase alfa and instead suggests that a simplified listing (such as the listing recently recommended for inhaled tobramycin powder) may be more appropriate. The submission offered two alternate wordings:

"Confirmed diagnosis of CF"

OR

“Cystic fibrosis. Patients must be 6 years of age and older with an FEV1 > 30% pred. Patient must be assessed at a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis.”

The submission provided no evidence to support the efficacy, safety and cost-effectiveness of DPI mannitol in broader cystic fibrosis populations.

- 2.11 Overall, the changes proposed in the submission appeared to be more focused on broadening the eligible patient population rather than reducing the complexity of the current PBS restriction. The Pre-PBAC Response stated that the proposed changes suggested by the sponsor are primarily to simplify the wording of the current listing and to allow concurrent or intermittent use of DPI mannitol and dornase alfa in patients for whom this combination is clinically appropriate.

For more detail on PBAC’s view, see section 5 “PBAC outcome”

3 Background

- 3.1 DPI mannitol is TGA registered for the ‘treatment of 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’.
- 3.2 There have been four previous PBAC submissions and one DUSC review for DPI mannitol.

Previous PBAC considerations of DPI mannitol

PBAC meeting	Details
March 2011	<p>Purpose: Requested listing of DPI mannitol for the treatment of cystic fibrosis in both paediatric (six years and above) and adult populations as either add on therapy to dornase alfa or in patients intolerant to, or inadequately responsive to dornase alfa.</p> <p>Comparator: Dornase alfa</p> <p>Evidence base: Direct comparison of DPI mannitol vs. dornase alfa vs. DPI mannitol/dornase alfa combination therapy (CF-203). Post-hoc subgroup analysis of DPI mannitol vs. control in dornase users/non-users (CF-301, CF-302). Indirect comparison of DPI mannitol (CF-301, CF-302) vs. dornase alfa (Fuchs 1994). Main outcomes: lung function measures and exacerbations.</p> <p>Clinical claim: The submission described DPI mannitol as similar in terms of efficacy and safety compared to dornase alfa. The submission described DPI mannitol in combination with dornase alfa as superior in terms of efficacy but inferior in terms of safety compared to dornase alfa alone.</p> <p>Economic evaluation: Cost minimisation analysis of DPI mannitol monotherapy (400mg twice a day) vs. dornase alfa (2.5mg once a day). Cost utility analysis of DPI mannitol/dornase alfa combination therapy vs. dornase alfa alone (ICER \$45,000 - \$75,000 per QALY gained).</p> <p>PBAC recommendation: Rejected. Main issues included: uncertain clinical place in therapy, uncertain main comparator (dornase alfa or nebulised hypertonic saline), uncertain effectiveness of DPI mannitol, uncertain cost-effectiveness.</p>
November 2011	<p>Purpose: Requested listing of DPI mannitol monotherapy for the treatment of cystic fibrosis as an alternative to dornase alfa in patients who have previously failed PBS-subsidised initiation criteria for dornase alfa; in patients who have discontinued dornase alfa despite a previous successful trial but were considering recommencing therapy; in patients currently on dornase alfa where a change of therapy might improve outcomes based on clinical global assessment.</p> <p>Comparator: Dornase alfa</p> <p>Evidence base: Pooled analysis of individual patient data for DPI mannitol vs. control in non-</p>

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PBAC meeting	Details
	<p>dornase users (CF-301, CF-302). Additional post-hoc subgroup analysis of DPI mannitol vs. control in patients intolerant/unresponsive to dornase alfa (CF-301, CF-302). Indirect comparison of DPI mannitol in non-dornase users (CF-301, CF-302) vs. dornase alfa (Fuchs 1994). Main outcomes: lung function measures and exacerbations. Additional efficacy and safety data from longer-term extension studies up to 78 weeks.</p> <p>Clinical claim: The submission described DPI mannitol as non-inferior in terms of efficacy and similar in terms of safety compared to dornase alfa.</p> <p>Economic evaluation: Weighted cost minimisation analysis of DPI mannitol monotherapy (400mg twice a day) vs dornase alfa (2.5mg once a day, 79% of use) and nebulised hypertonic saline (assumed no cost for this therapy, 21% of use)</p> <p>PBAC recommendation: Rejected. Main issues included: uncertain clinical place in therapy, uncertain main comparator (dornase alfa or nebulised hypertonic saline), uncertain effectiveness of DPI mannitol, uncertain cost-effectiveness.</p>
<p>March 2012 (minor)</p>	<p>Purpose: Requested listing of DPI mannitol monotherapy for the treatment of cystic fibrosis in patients who fail initiation criteria for dornase alfa; patients using dornase alfa intermittently; patients who are using dornase alfa, but are inadequately responsive, and it is considered may improve with DPI mannitol as an alternative to dornase alfa.</p> <p>Evidence base: No new data presented. The submission sought to address uncertainty regarding place in therapy (argued that therapy is tailored to individual patient needs) and main comparator (argued that hypertonic saline is an unregistered product that is not frequently used in Australia).</p> <p>Economic evaluation: Weighted cost minimisation analysis of DPI mannitol monotherapy (400mg twice a day) vs dornase alfa (2.5mg once a day, 70% of use) and nebulised hypertonic saline (assumed no cost for this therapy, 30% of use). The sponsor offered to provide access to combination therapy through a compassionate access program.</p> <p>PBAC recommendation: Recommended.</p>
<p>March 2013 (minor)</p>	<p>Purpose: Requested an amendment to the PBS listing to simplify treatment continuation rules (i.e. removal of continuation rules or replace 10% FEV1 improvement rule with a 'global consensus' assessment of treatment benefit by the patient/family and physician).</p> <p>Evidence base: No new data presented. The submission argued that changing the continuation rule in the restriction for DPI mannitol would improve patient access and better align the PBS listing with clinical practice and the clinical trial evidence.</p> <p>PBAC recommendation: Deferred, to seek further advice from Cystic Fibrosis Special Interest Group of the Thoracic Society of Australia and New Zealand (TSANZ).</p> <p>PBAC recommendation: Recommended an amendment to both the DPI mannitol and dornase alfa listings in July 2013, changing the continuation criteria to patients who demonstrate no deterioration in FEV1 compared to baseline; AND the patient or the patient's family (in the case of paediatric patients) must report improvement in the patient's airway clearance; AND the treating physician(s) must report a benefit in the clinical status of the patient.</p>
<p>October 2014 (DUSC review)</p>	<p>Purpose: To examine the utilisation of dornase alfa and DPI mannitol for cystic fibrosis, including a predicted versus actual (PvA) analysis of DPI mannitol in its first year of listing on the Pharmaceutical Benefits Scheme (PBS).</p> <p>Key findings: In the 12 months from May 2013 to April 2014, less than 10,000 patients received dornase alfa and less than 10,000 patients received DPI mannitol on the PBS. The utilisation of DPI mannitol in its first year of listing was lower than expected. The utilisation of dornase alfa has increased steadily since 2004.</p> <p>Discussion: DUSC considered that the lower than expected utilisation of DPI mannitol may be affected by the need for bronchial hyper-responsiveness testing; treatment burden (20 capsules per day); patient/physician preference for nebulised hypertonic saline; confusion about what constitutes combination therapy with dornase alfa; as well as international regulatory concerns regarding the lack of efficacy, incidence of haemoptysis and uncertain risk/benefit ratio in children. DUSC disagreed with the sponsor that the complexity of the restriction was limiting utilisation.</p> <p>Outcome statement: DUSC requested that advice be sought from cystic fibrosis physicians regarding the low uptake of DPI mannitol and that this advice be provided to the PBAC.</p>

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from the Thoracic Society of Australia and New Zealand (TSANZ) on the current listing of DPI mannitol. The TSANZ noted that the current restrictions are not felt to be in the best interests of patients with CF or their clinicians, as current clinical practice involves the use of multiple therapies in combination or sequentially to enhance mucus clearance in CF patients. The TSANZ further stated that they support the co-administration or sequential use of inhaled mannitol and dornase alfa and encourage a simplification of the criteria regarding the use of these agents (as outlined in section 2). The PBAC was supportive of the simplification of the restriction for mannitol; however, the Committee did not consider they had evidence of cost-effectiveness in first-line use of mannitol or co-administered mannitol and dornase alfa.

For more detail on PBAC's view, see section 5 "PBAC outcome"

Clinical trials

- 4.3 No new clinical trials were presented in the minor submission.
- 4.4 No data were presented on the use of DPI mannitol from the national CF patient database. No data were presented on combination use of DPI mannitol and dornase alfa from the sponsor's compassionate access program.

Comparative effectiveness

- 4.5 The trial results remain unchanged from the previous submissions. Relevant results from the March 2011 and November 2011 submissions are reproduced below.
- 4.6 One small, open-label, crossover trial (12 week treatment phases with 0-2 week washout periods) directly compared DPI mannitol vs. dornase alfa vs. DPI mannitol and dornase alfa combination in children with CF (CF-203). Combination therapy was defined as use of both treatments on the same day (DPI mannitol twice daily, dornase alfa once daily).

Table 1: Key outcomes reported in the head-to-head trial of DPI mannitol vs. dornase alfa vs. DPI mannitol/dornase alfa combination (CF-203)

Outcomes	DPI mannitol (N = 23)	Dornase alfa (N = 21)	DPI mannitol with dornase alfa (N = 23)
Mean change in FEV₁ (L) from baseline (SD)			
Baseline	1.74 (0.64)	1.61 (0.59)	1.66 (0.42)
Endpoint	1.82 (0.64)	1.72 (0.56)	1.66 (0.59)
Mean change (% change from baseline)	6.38%	9.07%	-0.77%
DPI mannitol vs dornase alfa (p value)			0.5632
DPI mannitol with dornase alfa vs dornase alfa (p value)			0.1337
Proportion of patients with PDPE events [n (%)]			
Endpoint	3 (14.3)	3 (13.0)	6 (26.1)
DPI mannitol vs dornase alfa (p value)			1.0000
DPI mannitol with dornase alfa vs dornase alfa (p value)			0.2568

Abbreviations: PDPE, protocol defined pulmonary exacerbation; SD, standard deviation; SE, standard error
Source: adapted from March 2011 PBAC meeting minutes and PES commentary

- 4.7 The PBAC previously noted that there were no statistically significant differences in lung function, protocol-defined pulmonary exacerbation (PDPE) events or respiratory quality of life scores between treatment groups. However, the combination of DPI mannitol and dornase alfa appeared to perform worse than either treatment administered separately (March 2011 PBAC public summary document (PSD)).
- 4.8 The efficacy of concomitant therapy was also assessed in post-hoc subgroup analyses of dornase alfa users and non-users in the pivotal DPI mannitol trials (CF-301, CF-302). These were multi-centre, parallel-group, double-blind trials comparing DPI mannitol with sub-therapeutic mannitol (as a control arm) in adults and children with CF over a 26 week duration. Categorisation of dornase alfa users/non-users was based on whether patients were 'routinely' using dornase alfa at baseline.

Table 2: Key outcomes reported in the dornase alfa users/non-users subgroups of the DPI mannitol vs. control trials (CF-301, CF-302)

Trial ID	Dornase alfa users			Dornase alfa non-users		
	DPI mannitol	Control	Difference	DPI mannitol	Control	Difference
Overall change (averaged over Week 6-26) in FEV₁ (%) from baseline (SE)						
CF-301 (N = 324)	4.47 (1.17)	1.59 (1.37)	2.88 (1.75) <i>p</i> = 0.101	7.98 (1.29)	3.46 (1.49)	4.53 (1.93) <i>p</i> = 0.020
CF-302 (N = 318)	6.50 (1.56)	2.90 (1.72)	3.59 (1.95) <i>p</i> = 0.066	10.43 (2.23)	5.27 (2.72)	5.16 (3.99) <i>p</i> = 0.129
Meta-analysis of dornase alfa users (PES commentary)			3.20 (1.30) <i>p</i> = 0.014 <i>I</i> ² = 0	Meta-analysis of dornase alfa non-user (PES commentary)		4.65 (1.74) <i>p</i> = 0.007 <i>I</i> ² = 0
Mean change in FEV₁ (%) from baseline to Week 26 (SE)						
CF-301 (N = 324)	4.48 (1.52)	-0.75 (1.74)	5.23 (2.28) <i>p</i> = 0.023	8.79 (1.64)	4.45 (1.94)	4.34 (2.52) <i>p</i> = 0.086
CF-302 (N = 318)	6.80 (1.83)	2.14 (2.05)	4.66 (2.45) <i>p</i> = 0.058	10.77 (2.74)	6.24 (3.40)	4.52 (4.27) <i>p</i> = 0.290
Meta-analysis of dornase alfa users (PES commentary)			4.97 (1.67) <i>p</i> = 0.002 <i>I</i> ² = 0	Meta-analysis of dornase alfa non-user (PES commentary)		4.39 (2.17) <i>p</i> = 0.043 <i>I</i> ² = 0
Mean annualised rate of PDPE events per patient (SD or 95% CI)						
CF-301 (N = 324)	1.05 (2.29)	1.19 (2.30)	RR 0.76 (0.45, 1.27)	0.47 (1.48)	0.86 (1.93)	RR 0.59 (0.24, 1.47)
CF-302 (N = 318)	0.53 (0.37, 0.75)	0.43 (0.27, 0.67)	RR 1.09 (0.61, 1.95)	0.18 (0.07, 0.49)	0.74 (0.40, 1.37)	RR 0.34 (0.10, 1.09)
Meta-analysis of dornase alfa users (PES commentary)			RR 0.89 (0.61, 1.31) <i>I</i> ² = 0	Meta-analysis of dornase alfa non-user (PES commentary)		RR 0.48 (0.23, 0.99) <i>I</i> ² = 0
Mean annualised rate of PE events per patient (SD or 95% CI)						
CF-301 (N = 324)	1.82 (2.80)	2.18 (2.75)	RR 0.76 (0.55, 1.06)	1.37 (2.79)	1.51 (2.16)	RR 0.94 (0.55, 1.60)
CF-302 (N = 318)	2.36 (2.00, 2.78)	2.20 (1.80, 2.68)	RR 1.00 (0.77, 1.30)	1.33 (0.92, 1.91)	2.22 (1.55, 3.17)	RR 0.69 (0.41, 1.16)
Meta-analysis of dornase alfa users (PES commentary)			RR 0.90 (0.73, 1.10) <i>I</i> ² = 39%	Meta-analysis of dornase alfa non-user (PES commentary)		RR 0.80 (0.55, 1.16) <i>I</i> ² = 0

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in first second of expiration; NR, not reported; PDPE, protocol defined pulmonary exacerbation; PE, pulmonary exacerbation; RR, rate ratio; SD, standard deviation; SE, standard error

Source: adapted from March 2011 PBAC meeting minutes and PES commentary

- 4.9 The PBAC previously noted that DPI mannitol treatment was associated with a statistically significant improvement in lung function compared to control in patients receiving concomitant dornase alfa and in patients not receiving concomitant dornase alfa.
- 4.10 DPI mannitol treatment was associated with a statistically significant decrease in PDPE rates compared to control in patients not using concomitant dornase alfa (although the wide confidence intervals raise uncertainty regarding the magnitude of effect). There was no statistically significant difference in PE rates between treatment groups in patients not using concomitant dornase alfa.

- 4.11 There was no statistically significant difference in exacerbation rates between DPI mannitol and control in patients using concomitant dornase alfa (March 2011 PBAC PSD).
- 4.12 A revised subgroup analysis of dornase users/non-users was included in the November 2011 submission based on a pooled analysis of individual patient data (see table 3). The PBAC did not formally consider comparisons between the two patient groups as the November 2011 submission requested listing of DPI mannitol as monotherapy in non-dornase users only. The results of the revised analysis were broadly consistent with the previous meta-analysis of reported trial data.

Table 3: Key outcomes reported in the dornase alfa users/non-users subgroups of the DPI mannitol vs. control trials (CF-301, CF-302)

Trial ID	Dornase alfa users			Dornase alfa non-users		
	DPI mannitol	Control	Difference	DPI mannitol	Control	Difference
Overall change (averaged over Week 6-26) in FEV₁ (%) from baseline (SE)						
CF-301 (N = 324)	4.67 (2.33, 7.01)	1.28 (-1.44, 4.01)	3.39 (-0.11, 6.88)	8.02 (5.46, 10.58)	3.51 (0.54, 6.48)	4.52 (0.65, 8.38)
CF-302 (N = 318)	6.50 (3.42, 9.57)	2.90 (-0.48, 6.29)	3.59 (-0.23, 7.42)	10.43 (6.04, 14.82)	5.27 (-0.10, 10.63)	5.16 (-1.51, 11.84)
Pooled analysis of dornase alfa users			3.14 (0.50, 5.78)	Pooled analysis of dornase alfa non-users		4.88 (1.24, 8.51)
Proportion (%) of patients with PDPE events						
CF-301 (N = 324)	22/96 (22.9)	21/67 (31.3)	RR 0.76 (0.45, 1.27)	10/81 (12.3)	12/51 (23.5)	RR 0.59 (0.24, 1.47)
CF-302 (N = 318)	24/137 (17.5)	16/92 (17.4)	RR 1.09 (0.61, 1.95)	4/47 (8.5)	7/29 (24.1)	RR 0.34 (0.10, 1.09)
Pooled analysis of dornase alfa users			1.03 (0.70, 1.51)	Pooled analysis of dornase alfa non-users		RR 0.58 (0.31, 1.07)
Proportion (%) of patients with PE events						
CF-301 (N = 324)	39/96 (40.6)	37/67 (55.2)	RR 0.76 (0.55, 1.06)	26/81 (32.1)	23/51 (45.1)	RR 0.94 (0.55, 1.60)
CF-302 (N = 318)	86/137 (62.8)	58/92 (63.0)	RR 1.00 (0.77, 1.30)	20/47 (42.6)	18/29 (62.1)	RR 0.69 (0.41, 1.16)
Pooled analysis of dornase alfa users			NR	Pooled analysis of dornase alfa non-users		NR

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in first second of expiration; NR, not reported; PDPE, protocol defined pulmonary exacerbation; PE, pulmonary exacerbation; RR, rate ratio; SD, standard deviation; SE, standard error

Source: adapted from November 2011 PBAC meeting minutes and PES commentary

Comparative harms

- 4.13 The trial results remain unchanged from the previous major submissions in March 2011 and November 2011. There was limited available information on the safety of combination therapy with DPI mannitol and dornase alfa.

Economic analysis

- 4.14 No economic comparison was presented in the minor submission. Given the small incremental benefit (or possible harm) associated with DPI mannitol and dornase alfa

combination therapy it is unlikely that the use of these two high cost therapies together would be considered cost-effective.

Drug cost/patient/year:

- 4.15 The annual drug cost for DPI mannitol is \$11,315 (\$1,736 [public hospital DPMQ] / 56 [days covered per script] x 365 [days per year]).
- 4.16 The annual drug cost for dornase alfa is \$14,357 (\$2,360 [public hospital DPMQ] / 60 [days covered per script] x 365 [days per year]).
- 4.17 The annual drug cost for DPI mannitol with dornase alfa is \$25,672.

Estimated PBS usage & financial implications

- 4.18 The submission noted the results of the DUSC predicted versus actual (PvA) from October 2014, which indicated that the actual utilisation of DPI mannitol on the PBS was substantially lower than predicted by the sponsor. The submission suggested that the lower than expected utilisation was due to three main factors: product features ('fiddly' delivery system), tolerability (main therapeutic action causes coughing) and complex PBS restriction. DUSC previously considered that the lower than expected utilisation of DPI mannitol may be affected by the need for bronchial hyper-responsiveness testing; treatment burden (20 capsules per day); patient/physician preference for nebulised hypertonic saline; confusion about what constitutes combination therapy with dornase alfa; as well as international regulatory concerns regarding the lack of efficacy, incidence of haemoptysis and uncertain risk/benefit ratio in children. DUSC previously disagreed with the sponsor that the complexity of the restriction was limiting utilisation given that dornase alfa has demonstrated sustained growth in the market despite having a similarly complex restriction as DPI mannitol.
- 4.19 The submission presented revised utilisation estimates based on the budget impact model presented in the November 2011 submission, updated with the following changes:
- Patient numbers have been reduced so that the predicted patients in Year 2 match the actual number of patients reported in the DUSC analysis.
 - Packs dispensed per patient have been reduced based on the assumption of 34% adherence which was derived from actual patient data from the DUSC analysis and actual pack data from sponsor's internal sales records.
 - Estimates are presented with and without patients currently receiving combination therapy through the sponsor's compassionate access program.

Table 4: Estimated utilisation of DPI mannitol and cost to the PBS in the first five years of listing

	Year 1	Year 2	Year 3	Year 4	Year 5
November 2011 budget impact model					
Treated patients					
Total packs (100% adherence)					
Total cost to PBS	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Total cost to government	\$	\$	\$	\$	\$
DUSC utilisation analysis (May 2013-April 2014)					
Treated patients		106	-	-	-
Total packs		821	-	-	-
Total cost to government		\$352,929	-	-	-
Revised budget impact model without combination use					
Treated patients					
Total packs (34% adherence)					
Total cost to PBS	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Total cost to government	\$	\$	\$	\$	\$
Revised budget impact model with combination use					
Treated patients					
Total packs (34% adherence)					
Total cost to PBS	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Total cost to government	\$	\$	\$	\$	\$
Net cost of expanding PBS listing to include combination use					
Net cost to the PBS	-	-	\$	\$	\$

4.20 The cumulative net cost associated with expanding the PBS listing to include combination therapy was estimated to be less than \$10 million over the next 3 years.

The revised utilisation/financial estimates were uncertain due to the following issues:

- The submission does not adjust patient numbers for differences in reporting periods between actual data and predicted estimates (DPI mannitol was listed on the PBS in August 2012 and therefore the DUSC analysis overlaps both Year 1 and Year 2 estimates).
- The submission has calculated a treatment adherence figure for mannitol from the data in the DUSC analysis. The data presented in the DUSC analysis is not appropriate for calculating treatment adherence. The adherence figure is likely to be an underestimate because the report data do not show when patients started treatment. As a result, fully adherent patients who started treatment part way through the year would be considered uncompliant. This will underestimate future utilisation.
- The submission used internal sales data rather than PBS data to estimate number of packs dispensed (less than 10,000 packs). This may artificially inflate adherence estimates as patient numbers are based on PBS-use while pack numbers are likely based on both PBS and non-PBS use.
- The submission assumed that adherence patterns for combination use would be the same as adherence patterns for monotherapy use. This assumption was inadequately justified.

- The submission assumed that the patient group using combination therapy will remain stable over time. This assumption was inadequately justified particularly given that the patient group using monotherapy was assumed to continue to grow over time.

4.21 At year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million per year.

4.22 The submission proposed that current risk share arrangements remain in place with no changes to previously agreed market volume caps.

For more detail on PBAC's view, see section 5 "PBAC outcome"

5 PBAC Outcome

5.1 The PBAC did not recommend amending the current listing of DPI mannitol to permit the combination use of DPI mannitol with dornase alfa on the basis of unproven cost-effectiveness. However, the PBAC did recommend some amendments to reduce the complexity of the DPI mannitol restriction.

5.2 The PBAC welcomed the input provided by the TSANZ suggesting that some patients may derive additional benefit with combined use of mannitol and dornase alfa, but noted that no price offer had been made to establish cost-effectiveness in this setting.

5.3 The PBAC did not accept the request to remove the criteria that patients must be intolerant to, or inadequately responsive to dornase alfa. In making this decision, the PBAC considered that removal of this criterion may result in mannitol being used as first line therapy, which was not supported by the available evidence.

5.4 The PBAC did not accept the request to remove the criteria that patients must be 6 years of age or older, based on a lack of clinical data in this age group.

5.5 The PBAC accepted that simplification of other elements of the restriction criteria, as outlined in section 2, was reasonable and agreed to remove or alter a number of criteria. Of note, the PBAC agreed to remove the criterion relating to FEV₁, the criterion requiring lung function testing and the grandfather clause. See the recommended listing for further details.

5.6 The PBAC advised that DPI mannitol is not suitable for prescribing by nurse practitioners.

5.7 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

5.8 The PBAC noted that the dornase alfa restriction should be re-examined out of session to allow common changes to be made, therefore aligning the DPI mannitol and dornase alfa restrictions where possible.

5.9 The PBAC noted that this submission is not eligible for an Independent Review. Independent Review is not available in response to a request to modify or extend an existing listing

Outcome:

Rejected

6 Recommended listing

6.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty packs	No. of Rpts	Proprietary Name and Manufacturer
MANNITOL Pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers, 1	4	5	Bronchitol® Pharmaxis

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Cystic fibrosis
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (Private hospital) <input checked="" type="checkbox"/> Streamlined (Public hospital)
Clinical criteria:	Patient must have been assessed for bronchial hyperresponsiveness as per the TGA approved Product Information mannitol initiation dose assessment, prior to mannitol therapy, with a negative result; AND Patient must be intolerant or inadequately responsive to dornase alfa.

Population criteria:	<p>Patient must be 6 years of age or older.</p> <p>Patient must be assessed at a cystic fibrosis clinic/centre which is under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis or by a specialist physician or paediatrician in consultation with such a unit.</p> <p>Prior to mannitol therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease.</p> <p>Initial therapy is limited to 3 months treatment with mannitol at a dose of 400 mg twice daily.</p> <p>To be eligible for continued PBS-subsidised treatment with mannitol following 3 months of initial treatment:</p> <p>(1) the patient must demonstrate no deterioration in FEV1 compared to baseline; AND</p> <p>(2) the patient or the patient's family (in the case of paediatric patients); AND</p> <p>(3) the treating physician(s) must report a benefit in the clinical status of the patient.</p> <p>Further reassessments must be undertaken and documented at six-monthly intervals. Mannitol therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.</p>
Population criteria:	<p>Patient must be 6 years of age or older.</p>
Prescriber Instructions	<p>Note It is highly desirable that all patients be included in the national cystic fibrosis patient database.</p> <p>Note Mannitol is not PBS-subsidised for use in combination with PBS-subsidised dornase alfa.</p>

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

Pharmaxis is disappointed that the PBAC could not recommend a change to amend the Bronchitol listing to bring it in line with best clinical practice. Pharmaxis welcomes the PBACs recommendation of simplification of the current wording and

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will continue to look at ways to amend the current listing to enable Bronchitol to be used in addition to best supportive care for appropriate patients.