PUBLIC SUMMARY DOCUMENT

Product: Mannitol, capsule containing powder for oral inhalation, 40 mg (for use in inhaler device), Bronchitol®

Sponsor: Pharmaxis Ltd

Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission requested an Authority Required listing for the treatment of cystic fibrosis (CF):

- as an alternative to dornase alfa in a patient who has previously failed PBS-subsidised initiation criteria for dornase alfa; OR
- as a monotherapy alternative to dornase alfa in a patient who has discontinued dornase alfa despite a previous successful trial and is considering recommencing therapy; OR
- as a monotherapy alternative to dornase alfa in a patient currently on dornase alfa or where a change of therapy might improve outcome based on clinical global assessment.

2. Background

At the March 2011 meeting, the PBAC rejected the submission because the comparator when dornase alfa has failed was inappropriate and because of uncertain effectiveness and resulting uncertain cost effectiveness, when used in combination with dornase alfa.

The PBAC considered the clinical place of mannitol was uncertain and questioned the applicability of the trial populations to the proposed PBS listings and overall, considered the evidence to support the proposed listings was uncertain. The PBAC was not convinced that combination use of these drugs would not lead to worse outcomes. Although acknowledging that trial CF-203 was underpowered and the larger trials of CF-301/CF-302, which had subgroups of patients on either both treatments or mannitol monotherapy, did not show a consistent trend of patients performing worse when the using mannitol in combination with dornase alfa, the benefit of mannitol as an add-on therapy remains uncertain. Trial data also did not support the monotherapy listing for patients who had failed to achieve an adequate response to dornase alfa. The indirect comparison with Fuchs (1994) is highly uncertain because of a lack of exchangeability and differences in the outcome measures between the trials.

The PBAC noted that the cost-minimisation in the monotherapy setting remained highly uncertain, even with the offer of a lower price than dornase alfa.

3. Registration Status

Mannitol powder for inhalation (Bronchitol®) was TGA registered on 11 March 2011 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.

Mannitol powder for inhalation was designated an orphan drug by the TGA on 16 April 2009 for use in the treatment of patients with cystic fibrosis to improve lung function and reduce pulmonary exacerbations.
4. Listing Requested and PBAC’s View

The submission proposed two listings, Option A and B.

**Option A**

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

**Private Hospital Authority Required**

Use by cystic fibrosis patients who satisfy all of the following criteria:
1. are 6 years of age or older;
2. Have a FEV1 greater than 30% predicted for age, gender and height
3. are intolerant or inadequately responsive to dornase alfa
4. 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);

**Private Hospital Authority Required**

**PATIENTS WHO ARE NOT CURRENTLY ON DORNASE ALFA**

Treatment of cystic fibrosis patients who;
1. have previously trialled and not met subsidisation criteria for Dornase alfa
2. Are intolerant to dornase alfa
3. Do not continue dornase alfa after clinical assessment

In order for patients to be eligible for participation in the HSD program, the following conditions must be met:
1. Patients must be assessed at cystic fibrosis clinics/centres which are under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis and the prescribing of mannitol powder for inhalation therapy under the HSD program is limited to such physicians. If attendance at such units is not possible because of geographical isolation, management (including prescribing) may be by specialist physician or paediatrician in consultation with such a unit;
2. The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;
3. Prior to mannitol powder for inhalation therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease;
4. Patients must be assessed for bronchial hyperresponsiveness as per TGA approved PI Bronchitol Initiation Dose Assessment. If the patient has a positive hyperresponsiveness test they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.
5. Initial therapy is limited to 4 weeks' treatment with Bronchitol at 400mg BD;
6. At or towards the end of the initial 4 weeks' trial, patients must be reassessed and a further FEV1 measurement be undertaken (single test under conditions as above). Patients who achieve a 10% or greater improvement in FEV1 (compared to baseline established prior to mannitol for inhalation treatment) are eligible for continued subsidy under Section 85 at a dose of 400mg BD;
7. Patients who fail to meet a 10% or greater improvement in FEV1 after the initial 4 weeks' treatment at a dose of 400mg BD, may have 1 further trial in the next 12 months but not before 3 months after the initial trial;
8. Following an initial 6 months' therapy, a global assessment must be undertaken involving the patient, the patient's family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that mannitol powder for inhalation treatment is continuing to produce worthwhile benefits. (Mannitol powder for inhalation therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;
9. Other aspects of treatment, such as physiotherapy, must be continued;
10. Where there is documented evidence that a patient already receiving mannitol powder for inhalation therapy would have met the criteria for subsidy (i.e. satisfied the criteria for the 4 week trial and achieved a 10% or greater improvement in FEV1) then the patient is eligible to continue treatment under Section 85. 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).

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.
Private Hospital Authority Required
TREATMENT OF CYSTIC FIBROSIS PATIENTS CURRENTLY TAKING DORNASE ALFA

In order for patients to be eligible for participation in Section 85, the following conditions must be met:
(1) Patients must have been taking dornase alfa for at least 6 months;
(2) Following an initial 6 months’ therapy of dornase alfa, a global assessment must be undertaken involving the patient, the patient’s family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that greater improvement in FEV1 could be achieved by switching to mannitol powder for inhalation. (Mannitol powder for inhalation therapy should not be commenced if there is not general agreement that greater FEV1 improvement could be attained or if there is a possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;
(3) The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;
(4) Prior to mannitol for inhalation therapy, a baseline measurement of FEV1 must be undertaken during a stable period of the disease;
(5) Patients must be assessed for Bronchitol hyperresponsiveness as per TGA approved PI Mannitol Tolerance Test. If the patient is hyperresponsive to mannitol they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.
(6) Initial therapy is limited to 4 weeks’ treatment with Bronchitol at 400 mg BD;
(7) At or towards the end of the initial 4 weeks' trial, patients must be reassessed and a further FEV1 measurement be undertaken (single test under conditions as above). Patients who achieve a 10% or greater improvement in FEV1 (compared to first line dornase alfa therapy [established prior to mannitol for inhalation treatment]) are eligible for continued subsidy under Section 85 at a dose of 400mg BD;
(8) Patients who fail to meet a 10% or greater improvement in FEV1 (compared to first line dornase alfa therapy baseline after the initial 4 weeks' treatment at a dose of 400mg BD, may have 1 further add on trial in the next 12 months but not before 3 months after the initial trial;
(9) Other aspects of treatment, such as physiotherapy, must be continued;

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

Option B
Bronchitol is indicated for the treatment of cystic fibrosis (CF) in both paediatric and adult populations six years and above in patients intolerant of or inadequately responsive to dornase alfa

Private Hospital Authority Required
Use by cystic fibrosis patients who satisfy all of the following criteria:
(1) are 6 years of age or older;
(2) or are intolerant or inadequately responsive to dornase alfa

Private Hospital Authority Required
PATIENTS WHO ARE NOT CURRENTLY ON DORNASE ALFA

Treatment of cystic fibrosis patients who;
   (i) have previously trialled and not met subsidisation criteria for Dornase alfa
   (ii) Are intolerant to dornase alfa
   (iii) Do not continue dornase alfa after clinical assessment

In order for patients to be eligible for participation in Section 85, the following conditions must be met:
(1) Patients must be assessed at cystic fibrosis clinics/centres which are under the control of specialist respiratory physicians with experience and expertise in the management of cystic fibrosis and the prescribing of mannitol powder for inhalation therapy under Section 85 is limited to such physicians. If attendance at such units is not possible because of geographical isolation, management (including prescribing) may be by specialist physician or paediatrician in consultation with such a unit;
(2) The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;
(3) Patients must be assessed for Bronchitol hyperresponsiveness as per TGA approved PI Mannitol Tolerance.
Test. If the patient has a positive hyperresponsiveness test they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.

(4) Following an initial 6 months’ therapy, a global assessment must be undertaken involving the patient, the patient’s family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that mannitol powder for inhalation treatment is continuing to produce worthwhile benefits. (Mannitol powder for inhalation therapy should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;

(5) Other aspects of treatment, such as physiotherapy, must be continued;

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

Private Hospital Authority Required
TREATMENT OF CYSTIC FIBROSIS PATIENTS CURRENTLY TAKING DORNASE ALFA

In order for patients to be eligible for participation in Section 85, the following conditions must be met:

(1) Patients must have been taking dornase alfa for at least 6 months;

(2) Following an initial 6 months’ therapy of dornase alfa, a global assessment must be undertaken involving the patient, the patient’s family (in the case of paediatric patients) and the treating physician(s) to establish that all agree that greater improvement in FEV₁ could be achieved with the addition of mannitol powder for inhalation. (Mannitol powder for inhalation therapy should not be commenced if there is not general agreement that greater FEV₁ improvement could be attained or if there is a possibility of harm from unnecessary use.) Further reassessments are to be undertaken at six-monthly intervals;

(3) The measurement of lung function is to be conducted by independent (other than the treating doctor) experienced personnel at established lung function testing laboratories, unless this is not possible because of geographical isolation;

(4) Patients must be assessed for Bronchitol hyperresponsiveness as per TGA approved PI Mannitol Tolerance Test. If the patient is hyperresponsive to mannitol they must not be prescribed Mannitol powder for inhalation. Patients with negative tests may commence mannitol powder for inhalation therapy.

(5) Other aspects of treatment, such as physiotherapy, must be continued;

Note:
It is highly desirable that all patients be included in the national cystic fibrosis patient data-base.

For PBAC’s view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Cystic fibrosis (CF) is a common hereditary disease which affects the entire body, causing progressive disability and often early death. CF is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). This gene is required to regulate the components of sweat, digestive juices, and mucus. The aim of treatment of CF is to alleviate symptoms, improve quality of life and to slow the decline in lung function by improving airway clearance, eradicating or suppressing the growth of bacterial pathogens and attenuating airway inflammation.

By mid childhood, most patients have increased airway secretions, and enhancing mucus clearance is a major goal of therapy. Several strategies have been proven to be effective, including physiotherapy, local hydration with inhaled moisture, enzymes to break down the inflammatory cell products, anti-inflammatory agents and aggressive treatment of bacterial infections. In a proportion of patients, mucolytic agents are prescribed. Currently dornase alfa is the only mucolytic agent subsidised on the PBS for use in CF.

The submission proposed that the place in therapy of mannitol powder for inhalation is for patients 6 years of age or older who are intolerant or inadequately responsive to dornase alfa.
The PBAC agreed there is a clinical need for additional treatment options for patients with CF, however further consultation with clinicians is required to ascertain the appropriate clinical place in therapy of mannitol.

6. Comparator
The submission nominated dornase alfa as the comparator. This was not accepted by the PBAC in March 2011. The submission presented new sources of evidence to support its choice of comparator as follows:
1. Further background on the burden of treatment in CF and the need for an alternative to dornase alfa.
2. Evidence from the BIOGRID dataset that patients taking dornase alfa do have ‘on’ and ‘off’ treatment episodes.
3. Hypertonic saline manufacturing data for Australia.
4. Physician Survey data of dornase and hypertonic saline use in 8 out of 19 Australian CF clinics (treating more than 50% of Australian CF patients aged over 6 years).

The PBAC noted that dornase alfa, the comparator in the re-submission, was unchanged from the previous submission. The PBAC considered this to be inappropriate and that hypertonic saline or usual care (placebo) are appropriate comparators. The PBAC considered that there could be some substitution of dornase alfa by mannitol, and hence dornase alfa as part of a mixed comparison may be reasonable.

7. Clinical Trials
The re-submission presented four studies that were included in the March 2011 submission:
- one head-to-head trial comparing three treatment arms (dry powder inhaler (DPI) mannitol vs. dornase alfa vs. DPI mannitol plus dornase alfa combination) in children with cystic fibrosis (CF-203);
- two trials of DPI mannitol vs. control (sub-therapeutic mannitol) (CF-301, CF-302);
- one trial of dornase alfa vs placebo (Fuchs et al 1994) in children and adults with cystic fibrosis.

The re-submission also presented new results from unpublished open-label extensions of the CF-301 (up to 78 weeks follow-up) and CF-302 (up to 52 weeks follow-up) trials.

Details of the studies published at the time of submission are shown in the table below:

<table>
<thead>
<tr>
<th>Trial ID / First author</th>
<th>Protocol title / Publication title</th>
<th>Publication citation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mannitol vs. Dornase alfa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mannitol vs placebo</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8. Results of Trials

The re-submission primarily focused on forced expiratory volume in first second of expiration (FEV$_1$) and exacerbation (PDPE, protocol-defined pulmonary exacerbation) outcomes in the non-dornase user subgroups of the CF-301/CF-302 trials as these measures are used in an indirect comparison of DPI mannitol and dornase alfa.

The key FEV$_1$ outcomes reported in the DPI mannitol vs. control trials (CF-301, CF-302) are shown in the following table:

| Key FEV$_1$ outcomes reported in the DPI mannitol vs. control trials (CF-301, CF-302) |
|---|---|---|---|
| **Trial ID** | DPI mannitol | Control (sub mannitol) | Treatment effect |
| Overall change (Week 6-26) in FEV$_1$ (mL) from baseline (95% CI) | | | |
| CF-301 non-dornase user (N = 132) | 152.80 (106.87, 198.73) | 48.46 (-4.35, 101.27) | 104.34 (36.08, 172.61) |
| CF-302 non-dornase user (N = 76) | 142.31 (69.62, 215.00) | 55.81 (-32.86, 144.48) | 86.50 (-23.78, 196.79) |
| Pooled analysis of dornase alfa non-users | 96.50 (34.92, 158.07) | | |
| Overall change (Week 6-26) in FEV$_1$ (%) from baseline (95% CI) | | | |
| CF-301 non-dornase user (N = 132) | 8.02 (5.46, 10.58) | 3.51 (0.54, 6.48) | 4.52 (0.65, 8.38) |
| CF-302 non-dornase user (N = 76) | 10.43 (6.04, 14.82) | 5.27 (-0.10, 10.63) | 5.16 (-1.51, 11.84) |
| Pooled analysis of dornase alfa non-users | 4.88 (1.24, 8.51) | | |
| Overall change (Week 6-26) in FEV$_1$ (%) predicted from baseline (95% CI) | | | |
| CF-301 non-dornase user (N = 132) | 3.75 (2.35, 5.14) | 1.16 (-0.44, 2.76) | 2.59 (0.50, 4.67) |
| CF-302 non-dornase user (N = 76) | 4.51 (2.07, 6.95) | 1.73 (-1.26, 4.73) | 2.78 (-0.94, 6.50) |
| Pooled analysis of dornase alfa non-users | 2.63 (0.61, 4.64) | | |

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DPM-CF-302 2008
Aitken ML et al 2010
Six-month administration of inhaled mannitol in cystic fibrosis - A safety and efficacy study

Dornase alfa versus placebo

Fuchs et al. 1994
Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group

Also published as:
Shak 1995
Aerosolized recombinant human DNase I for the treatment of cystic fibrosis
Chest 107(2 Suppl): 65s-70s
Oster et al 1995
Economic analysis: Effects of recombinant human DNase therapy on healthcare use and costs in patients with cystic fibrosis
DPI mannitol was generally associated with modest improvements in lung function (FEV\textsubscript{1}) compared to control (difference of 4.88%; 95% CI 1.24%, 8.51%) in non-dornase users that was sustained over the 26 weeks of the studies. This improvement was statistically significant in the CF-301 trial and the pooled analysis but did not reach statistical significance in the CF-302 trial. The clinical importance of these changes in FEV\textsubscript{1} is unclear as the subjects had mean baseline FEV\textsubscript{1} around 65% of predicted values. The European Medicines Agency (EMA) recently raised concerns that the improvement in FEV\textsubscript{1} seen with DPI mannitol treatment may not be sufficient to improve the patients’ condition. The EMA also raised concerns that the improvement in FEV\textsubscript{1} was not consistent across all age groups (Bronchitol fact sheet, EMA/CHMP/474477/2011; EMEA/H/C/0012, 23rd June 2011).

Data from the open-label extensions suggested that FEV\textsubscript{1} improvements seen during the double-blind phase of the trials (26 weeks) may be maintained for at least 52 weeks. Patients previously treated with the control in the double-blind phase achieved similar FEV\textsubscript{1} results to the active treatment group when switched to DPI mannitol.

The re-submission acknowledged that both the CF-301 and CF-302 trials reported differential discontinuations between the DPI mannitol and control arms (CF-301: 34% vs. 25%; CF-302: 16% vs. 11%, respectively). Adverse events and withdrawal of consent appeared to be the main reasons for the difference in discontinuations. To address the potential impact of patient dropouts on the estimated treatment effect the re-submission presented multiple post-hoc analyses of FEV\textsubscript{1} outcome data from the CF-301 and CF-302 trials using various imputation methods. The re-submission claimed that the consistency of treatment effects across imputation methods demonstrated the validity of the methods used in the primary FEV\textsubscript{1} analyses.

The key exacerbation outcomes reported in the DPI mannitol vs. control trials (CF-301, CF-302) are shown in the following table:

<table>
<thead>
<tr>
<th>Proportion of patients with PDPE events [n/N (%)]</th>
<th>DPI mannitol</th>
<th>Control (sub mannitol)</th>
<th>Rate Ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF-301 non-dornase users</td>
<td>10/81 (12.3)</td>
<td>12/51 (23.5)</td>
<td>0.59 (0.24, 1.47)</td>
<td>0.59 (0.25, 1.38)</td>
</tr>
<tr>
<td>CF-302 non-dornase users</td>
<td>4/47 (8.5)</td>
<td>7/29 (24.1)</td>
<td>0.34 (0.10, 1.09)</td>
<td>NR</td>
</tr>
<tr>
<td>Pooled analysis of dornase alfa non-users</td>
<td>0.58 (0.31, 1.07)</td>
<td></td>
<td>0.44 (0.21, 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Individually, neither of the key trials demonstrated a statistically significant reduction in exacerbations with DPI mannitol therapy compared to control. A pooled analysis of non-dornase users suggested that DPI mannitol may reduce the risk of pulmonary exacerbations (HR 0.44, 95% CI 0.21, 0.94) however the pooled rate ratio did not reach statistical significance (RR 0.58, 95% CI 0.31, 1.07). These estimates were based on limited patient numbers with a small number of events and there are wide confidence intervals around each estimate. The re-submission did not address the potential impact of differential discontinuations on exacerbation outcomes which may limit the validity of the results.
The main analysis in the re-submission was an indirect comparison of the pooled DPI mannitol results (CF-301, CF-302) against dornase alfa (Fuchs et al 1994) using the control/placebo arms as a common comparator.

It should be noted that the DPI mannitol trials used a sub-therapeutic dose of mannitol in the control arm, whereas the dornase alfa trial were placebo-controlled.

A summary of the pooled DPI mannitol results (CF-301, CF-302) against dornase alfa (Fuchs et al 1994) using the control/placebo arms as a common comparator is shown in the following table:

### Summary of results from the indirect comparison

<table>
<thead>
<tr>
<th>Trial</th>
<th>DPI mannitol</th>
<th>Control/Placebo</th>
<th>Dornase alfa</th>
<th>Treatment effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall change in FEV₁ (%) from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF-301/CF-302 (non-dornase users)</td>
<td>9.4 (13.9)</td>
<td>4.6 (13.1)</td>
<td>-</td>
<td>4.9 (1.1, 8.7)</td>
</tr>
<tr>
<td>Fuchs (1994)</td>
<td>-</td>
<td>0 (10.8)</td>
<td>5.8 (12.6)</td>
<td>5.8 (4.0, 7.6)</td>
</tr>
<tr>
<td>Indirect estimate of effect [mean difference (95% CI)]</td>
<td>-0.9</td>
<td></td>
<td></td>
<td>(-5.1, 3.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of patients with PDPE events [n/N, (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF-301/CF-302 (non-dornase users)</td>
</tr>
<tr>
<td>Fuchs (1994)</td>
</tr>
<tr>
<td>Indirect estimate of effect (95% CI)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in one second; HR, hazard ratio; OR, odds ratio; PDPE, protocol defined pulmonary exacerbation; RR, relative risk
Note: Difference in FEV₁ treatment effect > 0 favours DPI mannitol

The indirect analysis did not demonstrate any statistically significant difference in FEV₁ outcomes between DPI mannitol and dornase alfa. DPI mannitol treatment was associated with a statistically significant reduction in exacerbations compared to dornase alfa in terms of relative risk and odds ratio but not hazard ratio. Based on the indirect analyses, the re-submission claimed that both DPI mannitol and dornase alfa are comparable in terms of improving lung function and reducing the risk of exacerbations. However, the PBAC considered it is unclear whether the study populations are sufficiently similar to justify an indirect analysis.

Patients in the non-dornase user subgroups of the CF-301 and CF-302 trials were generally older (23-24 years) with better lung function (FEV₁ approximately 65% of predicted) compared to patients enrolled in the Fuchs et al (1994) trial (age approximately 18-19 years, FEV₁ approximately 60% of predicted). Additionally, it is likely that the clinical management of cystic fibrosis patients has changed over time given that the dornase alfa trial was conducted approximately 10-15 years before the DPI mannitol trials. Improvements in lung
function and a reduction in exacerbations shown with DPI mannitol were achieved on top of these changes in treatment practices, including high levels of inhaled antibiotics.

Finally, the DPI mannitol trials reported relatively high discontinuation rates (approximately 30% in CF-301 and 15% in CF-302) compared to the dornase alfa trial (approximately 3%) which could suggest some underlying differences between trials that may limit any indirect comparison between treatments.

*For PBAC’s view of these results, see Recommendation and Reasons.*

The re-submission did not update the comparative safety data.

Similar proportions of patients in the DPI mannitol and control (sub-therapeutic mannitol) treatment arms experienced adverse events during the CF-301/CF-302 trials. Patients were more likely to experience treatment-related events in the DPI mannitol arm (mainly cough and haemoptysis) compared to control. DPI mannitol was also associated with a higher incidence of withdrawals due to adverse events compared to control. Adverse events associated with dornase alfa include: voice alteration, rash, haemoptysis, dyspnoea, pharyngitis and laryngitis.

The EMA recently raised concerns about the safety of DPI mannitol treatment, particularly with respect to narrowing of the airways in the lungs and haemoptysis.

During the evaluation, the sponsor provided additional adverse event data from the open-label extensions of CF-301 and CF-302. The most common treatment-related adverse events (possibly, probably or definitely related to DPI mannitol treatment) during the open-label extensions were cough, haemoptysis, wheezing, productive cough, asthma, dyspnoea, throat irritation, condition aggravated, bacteria sputum identified and headache.

*For PBAC’s view, see Recommendation and Reasons.*

### 9. Clinical Claim

The re-submission described DPI mannitol monotherapy as non-inferior to dornase alfa in terms of comparative effectiveness (FEV\textsubscript{1} outcomes) and similar in terms of comparative safety.

The re-submission also described DPI mannitol monotherapy as superior to placebo/control in terms of comparative effectiveness (FEV\textsubscript{1} outcomes) and inferior in terms of comparative safety. Although the submission presented a clinical claim against placebo/control, no economic analysis based on this claim was presented.

The PBAC considered that the indirect comparison of DPI mannitol (non-dornase users) and dornase alfa presented in the submission suggested that both therapies have similar treatment effects in terms of FEV\textsubscript{1} and exacerbations compared to control. However, it was unclear whether the study populations were sufficiently similar to justify an indirect analysis. Additionally, there were insufficient data to assess whether DPI mannitol and dornase alfa have comparable safety profiles.

### 10. Economic Analysis
The re-submission presented a cost minimisation analysis of DPI mannitol monotherapy vs. dornase alfa, and calculated a weighted price to account for some substitution of DPI mannitol for hypertonic saline (based on expected usage patterns).

Based on the indirect analysis, the equi-effective dose of DPI mannitol is 400 mg twice daily compared to dornase alfa 2.5 mg once daily.

*For PBAC’s view, see Recommendation and Reasons.*

11. **Estimated PBS Usage and Financial Implications**

The likely number of patients/year was estimated by the submission to be less than 10,000 in Year 5, similar to the previous submission.

A net financial saving/year to the PBS was estimated by the submission over the first 5 years compared to a financial cost/year in the previous submission. The financial implications are to be further verified.

*For PBAC’s view, see Recommendation and Reasons.*

12. **Recommendation and Reasons**

The PBAC considered that the clinical place of mannitol in the treatment of cystic fibrosis (CF) remains uncertain. The PBAC considered the extent to which mannitol, dornase alfa and hypertonic saline are used cyclically or in combination, which combinations are used and when treatments are added-on in clinical practice remains unclear. The PBAC considered the survey results referred to in the re-submission provided insufficient evidence to adequately inform the clinical place in therapy of mannitol. The PBAC agreed there is a clinical need for additional treatment options for patients with CF, however further consultation with clinicians is required to ascertain the appropriate clinical place in therapy of mannitol.

The PBAC noted that dornase alfa, the comparator in the re-submission, was unchanged from the previous submission. The PBAC considered this to be inappropriate and that hypertonic saline or usual care (placebo) are appropriate comparators. However a clinical comparison to hypertonic saline was not presented. The PBAC considered that there could be some substitution of dornase alfa by mannitol, and hence dornase alfa as part of a mixed comparison may be reasonable. The PBAC, however noted that the extent that mannitol would substitute for dornase alfa is uncertain.

The PBAC noted that the trials presented as clinical evidence were the same as in the previous submission with the addition of results from unpublished open-label extensions of the CF-301 and CF-302 trials. The PBAC noted that the re-submission presented limited data on hypertonic saline (the Cochrane review). No data addressing the comparative efficacy and safety of mannitol versus hypertonic saline or for switching from dornase alfa to mannitol was presented. The PBAC also noted that the results of the indirect comparison suggested that mannitol and dornase alfa have similar treatment effects in terms of FEV\textsubscript{1} and exacerbations when compared to control. However, patients enrolled in CF-301 and CF-302 and Fuchs 1994 were different populations, discontinuation rates were substantially different between the trials and the management of cystic fibrosis between when Fuchs study (1994) and CF-301 and CF-302 trials were conducted has probably changed.
The PBAC considered insufficient data was presented to assess whether mannitol and dornase alfa have comparable safety profiles. The PBAC noted that mannitol was associated with an increased risk of cough (25.4% vs 20.3%) and haemoptysis (11.9% vs 8.5%) compared to control.

The PBAC noted the submission presented a cost minimisation analysis of mannitol monotherapy versus dornase alfa. The PBAC considered the issues regarding the place in therapy of mannitol, the comparator and the clinical efficacy flowed into the economic evaluation. The PBAC noted that the weighted price proposed for mannitol was based on the assumption of substitution of dornase alfa and hypertonic saline, based on estimated usage patterns. The PBAC considered this was highly uncertain as the submission did not present any data on the comparative efficacy and safety to hypertonic saline. The sponsor provided survey results in its Pre-Sub Committee Response. However the PBAC noted that these results were not evaluated and the PBAC considered that they provided insufficient evidence to adequately support the substitution estimates.

The PBAC further noted that there was potential for use of mannitol outside the requested monotherapy PBS listing as add-on therapy, because the place in therapy of mannitol is uncertain and mannitol’s TGA registration includes add-on therapy.

The PBAC therefore rejected the submission because the comparator was inappropriate, and on the basis of uncertain clinical effectiveness and uncertain cost effectiveness.

**Recommendation:**
Reject

13. **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.

14. **Sponsor’s Comment**
Pharmaxis look forward to working with the PBAC to further reduce uncertainty, and to make a new treatment option available for Australian CF patients.