

## 7.05 MANNITOL

### Pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers Bronchitol®, Pharmaxis Ltd

#### 1 Purpose of Application

- 1.1 Mannitol is currently listed on the PBS as a Section 100, Authority Required listing for the treatment of patients with cystic fibrosis (CF) who are intolerant or inadequately responsive to dornase alfa (DNase).
- 1.2 The current resubmission requested to remove the NOTE in the current listings that prohibits PBS-subsidised use in combination with PBS-subsidised DNase. Thus, the listing requested was specifically for patients currently taking DNase who are inadequately responsive and wish to add on mannitol.

**Table 1: Key components of the clinical issue addressed by the resubmission**

| Component      | Description  |
|----------------|--|
| Population     | CF patients inadequately responsive to dornase alfa  |
| Intervention   | Mannitol + best supportive care (may or may not include dornase alfa)  |
| Comparator     | Placebo + best supportive care (may or may not include dornase alfa)   |
| Outcomes       | FEV <sub>1</sub> outcomes and pulmonary exacerbations (measured in the mannitol trials)  |
| Clinical claim | In CF patients who are inadequately responsive to dornase alfa, mannitol + best supportive care is more effective than placebo + best supportive care at improving FEV <sub>1</sub> outcomes |

Source: compiled during the evaluation. CF = cystic fibrosis, FEV<sub>1</sub> = forced expiratory volume in 1 second.

#### 2 Requested listing

- 2.1 The requested deletion to the current listing is crossed out with strikethrough and a suggested addition is in italics in the below.

| Name, Restriction, Manner of administration and form                               | Max. Qty   | No. of Rpts | Dispensed Price for Max. Qty (published)              | Proprietary Name and Manufacturer |
|--|--|-------------|---|-----------------------------------|
| MANNITOL   |  |             |   |                                   |
| Pack containing 280 capsules containing powder for inhalation 40 mg and 2 inhalers | 4  | 5           | \$ [REDACTED] * (Private)<br>\$ [REDACTED] # (Public) | Bronchitol® Pharmaxis             |
| <b>Category / Program</b>  | Section 100 – Highly Specialised Drugs Program   |             |   |                                   |
| <b>PBS Indication:</b>   | Cystic fibrosis  |             |   |                                   |
| <b>Restriction Level / Method:</b>   | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing (Private hospital)<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input checked="" type="checkbox"/> Streamlined (Public hospital) |             |   |                                   |

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|                                |   |
|--------------------------------|---|
| <b>Clinical criteria:</b>      | Patient must have been assessed for bronchial hyperresponsiveness as per the TGA approved Product Information initiation dose assessment for this drug, prior to therapy with this drug, with a negative result,<br>AND<br>Patient must be intolerant or inadequately responsive to dornase alfa.   |
| <b>Population criteria:</b>    | Patient must be 6 years of age or older.  |
| <b>Prescriber Instructions</b> | 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.<br><br>Prior to therapy with this drug, a baseline measurement of forced expiratory volume in 1 second (FEV1) must be undertaken during a stable period of the disease.<br><br>Initial therapy is limited to 3 months treatment with mannitol at a dose of 400 mg twice daily.<br><br>To be eligible for continued PBS-subsidised treatment with this drug following 3 months of initial treatment:<br>(1) the patient must demonstrate no deterioration in FEV1 compared to baseline; AND<br>(2) the patient or the patient's family (in the case of paediatric patients) and the treating physician(s) must report a benefit in the clinical status of the patient.<br><br>Further reassessments must be undertaken and documented at six-monthly intervals. Therapy with this drug should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use. |
| <b>Administrative Advice</b>   | <del>This drug is not PBS-subsidised for use in combination with PBS-subsidised dornase alfa.</del><br><br>It is highly desirable that all patients be included in the national cystic fibrosis patient database.<br><br><i>Patients should have been trialled with hypertonic saline in their treatment history before any combination use of mannitol and dornase alfa.</i>   |

\* New DPMQ with 5% price reduction from 1 April 2018 will be \$ [REDACTED]. The new effective DPMQ (following the mandatory 5% price cut due April 2018 and the [REDACTED]) is \$ [REDACTED].

# The new effective DPMQ (following the mandatory 5% price cut due April 2018 and the [REDACTED]) is \$ [REDACTED].

2.2 The requested basis for listing was cost-effectiveness compared with placebo (plus best supportive care, which may or may not include DNase). Given the requested restrictions, it was conceivable that only those patients already on DNase but obtaining inadequate response would initiate mannitol in combination therapy.

2.3 The Pre-Sub-Committee Response (PSCR) (p1) agreed to the addition of a NOTE in the PBS restriction stating "Patients should have been trialled with hypertonic saline in their treatment history before any combination use of mannitol and dornase alfa" (see paragraphs 5.3-4).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### 3 Background

- 3.1 Mannitol was TGA registered on 2 March 2011 for the treatment of CF in patients aged 6 years and above as either an add-on therapy to DNase or in patients intolerant to, or inadequately responsive to DNase.
- 3.2 There have been five previous submissions to the PBAC for mannitol. In March 2011, the PBAC considered a submission for mannitol as either monotherapy in those intolerant or unresponsive to DNase or as add on therapy in those inadequately responsive to DNase. The combination therapy part of the submission was supported by a cost utility model of mannitol + DNase vs. DNase alone. The PBAC considered the evidence in combination therapy with DNase to be uncertain with resulting uncertain cost effectiveness. Following a major resubmission in November 2011 and a minor resubmission in March 2012, mannitol was recommended for monotherapy on a cost minimisation basis versus 70% DNase and 30% hypertonic saline (cost assumed to be zero), and was implemented in August 2012.
- 3.3 In July 2015, the PBAC rejected a minor resubmission that requested combination use with DNase (via deletion of the NOTE prohibiting combined use in the restriction, as per the current resubmission). No new clinical or cost effectiveness data was presented in this minor resubmission. The PBAC did not recommend amending the current listing of mannitol to permit the combination use of mannitol with DNase on the basis of unproven cost-effectiveness.
- 3.4 Some outstanding matters to the PBAC and key elements from both the March 2011 submission and the July 2015 resubmission are summarised in Table 2.

**Table 2: Outstanding matters of concern to the PBAC and summary of the current resubmission and relevant past submissions**

| Component                    | March 2011 submission  | July 2015 minor resubmission   | Current resubmission  |
|------------------------------|--|--|---|
| Restriction                  | Part of the request was for add on therapy to DNase in those inadequately responsive. The other part was for monotherapy after failing DNase (which is now listed).    | Restriction: to remove the NOTE which prohibits combination therapy with DNase.  | Restriction: to remove the NOTE which prohibits combination therapy with DNase  |
| Comparator                   | DNase alone  | No comparator nominated  | Placebo + BSC (that may or may not include DNase)   |
| Main clinical evidence       | CF-301, CF302 and CF-203   | No new data was presented. The resubmission's arguments were based on arguments around a technicality between some misalignments between the TGA approved indication and the PBS restriction and that the requested additional population was small. The resubmission also had the intent of simplifying the restriction for mannitol to minimise confusion. | CF-301 and CF-302 including new long term open label phases. CF-203 was excluded in submission (included in evaluation). CF-204.    |
| Patient population in trials | Given the use of DNase in some, but not all patients in the two key trials (CF-301 and CF-302), the data used in the model was not appropriate (p9 of March 2011 PSD). |  | Not addressed in the resubmission, which uses efficacy results from the ITT population. The economic model also assumes that 65% of |

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| Component                    | March 2011 submission   | July 2015 minor resubmission  | Current resubmission  |
|------------------------------|---|---|---|
|                              |   |   | patients are on DNase, which does not correspond to the appropriate comparison in this resubmission.  |
| Clinical claim               | The submission described mannitol in combination with domase alfa as superior in terms of efficacy but inferior in terms of safety compared to domase alfa alone.<br>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 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 using mannitol in combination with DNase, the benefit of mannitol as an add-on therapy remains uncertain. | None presented.   | Mannitol + BSC is superior to BSC (which may include DNase) at improving FEV <sub>1</sub> outcomes. Same safety claim as March 2011 submission.   |
| Modelled economic evaluation | A cost utility model was presented comparing the costs and health outcomes associated with usual care, mannitol alone, DNase alone, and the combination of mannitol with DNase in patients with cystic fibrosis.<br><br>The model was dependent on a number of assumptions, such as maintenance of treatment effect, that were not well justified in the submission (p9 of March 2011 PSD).   | None presented  | A cost utility model was presented comparing the costs and health outcomes associated with mannitol + BSC (may or may not include DNase) versus placebo + BSC (may or may not include DNase). |
| Estimated cost to PBS        | Monotherapy and combination use: less than \$10 million in Year 5, total of \$10 – \$20 million over the first 5 years of listing.  | Combination use: less than \$10 million in Year 5, total of less than \$10 million over the first 5 years of listing. | Combination use: \$ less than \$10 million in Year 5, total of less than \$10 million over the first 5 years of listing.  |
| PBAC decision                | Reject – uncertain effectiveness and resulting uncertain cost effectiveness, when used in combination with DNase.   | Reject – unproven cost effectiveness, when used in combination with DNase.  | -   |

Source: Compiled during the evaluation

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 4 Population and disease

4.1 CF is a 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. This is achieved by improving airway clearance, by 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 (i.e. DNase) are prescribed.

- 4.2 DNase and mannitol are listed on the PBS as monotherapies, with mannitol as a second-line treatment for patients inadequately responsive or intolerant to DNase. A third option available to patients privately is inhaled hypertonic saline; it is a hyperosmotic agent like mannitol and works by drawing water into the lungs. Although hypertonic saline appears to be used throughout the disease course of CF, it can also be used in the later stages as an alternative by either replacing, or as an add-on therapy, to other mucous clearing agents. The resubmission requested the current restriction be changed to allow patients who are inadequately responsive to DNase to add on mannitol rather than to switch treatments.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **5 Comparator**

- 5.1 The resubmission proposed best supportive care (BSC), which may or may not include DNase, as the main comparator. The evaluation considered that a more appropriate comparison for mannitol + optimised DNase may have been placebo + optimised DNase (both against the background of other BSC therapies). The March 2011 submission nominated DNase as the appropriate comparator in the combination use setting.
- 5.2 The PSCR (p1) argued the submission seeks to enable all patients aged 6 years and over to obtain mannitol in combination with their standard care regimen, irrespective of whether their regimen includes DNase, and therefore the appropriate comparator is placebo/control + BSC. The ESC agreed with the evaluation that as the purpose of the resubmission was to request use in combination with DNase, and patients who are intolerant to DNase are already able to switch to PBS subsidised mannitol monotherapy, the appropriate comparator was placebo + optimised DNase.
- 5.3 Hypertonic saline, used throughout the disease course of CF, may also be a relevant comparator if additional restrictive wording is not added to ensure mannitol is only added to DNase after a failed trial of hypertonic saline. The PSCR (p1) argued that hypertonic saline is not an appropriate comparator because optimal treatment

regimens are not clearly defined and hypertonic saline should be trialled before combination use of mannitol and DNase. The PSCR (p1) agreed to the addition of a NOTE in the PBS restriction stating “Patients should have been trialled with hypertonic saline in their treatment history before any combination use of mannitol and dornase alfa” (see paragraph 2.3).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from individuals (18), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of combination treatment with mannitol with DNase including the improved airway clearance and decreased exacerbations of symptoms.

6.3 The PBAC noted the advice received from Cystic Fibrosis Australia and Cystic Fibrosis SA clarifying the likely use of mannitol in clinical practice. The PBAC specifically noted the advice that the use of mannitol in combination with dornase alfa, in some patients is the most effective regime. The PBAC also noted the concerns regarding equity of access, given that mannitol, if given in combination with PBS-subsidised DNase is currently only available via a compassionate use program, and only 9 of the 24 Australian CF centres participate in the program, which can make prescribing complex for clinicians and patients. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical trials***

6.4 The resubmission was based on four trials comparing mannitol to control/placebo:

- Two phase III trials comparing mannitol (400 mg twice daily) to a sub-therapeutic dose of mannitol (50 mg twice daily) as control (CF-301 and CF-302) (n=600);
- Two phase II trials comparing mannitol to placebo (CF-201 and CF-204) (n=134).

6.5 The previous March 2011 submission included Trials CF-301 and CF-302. It also included Trial CF-203, a head-to-head cross-over trial of mannitol + DNase versus the two agents administered as monotherapy, in children with CF, which was inappropriately excluded from this resubmission. The current resubmission also

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excluded Trial IIS-B-118 (Middleton et al. 2015) mainly on the basis of it being for a different indication (acute pulmonary exacerbations); however, the ESC noted that these patients would qualify for combination treatment within the proposed PBS restrictions. The March 2011 submission excluded Trial CF-201 on the basis of a higher than recommended dose of mannitol (420 mg twice daily), but this trial was included in this resubmission. The pre-PBAC response (p1) stated that the inclusion of Trial CF-203 in the evaluation is problematic as patients were not optimised on DNase treatment before the treatment period and additionally, due to the small sample size, no statistically differences in spirometry outcomes were observed.

6.6 Details of the trials presented in the resubmission are provided in Table 3.

**Table 3: Trials and associated reports presented in the resubmission**

| Trial ID   | Protocol title/ Publication title  | Publication citation   |
|--|--|--|
| <b>mannitol vs. control (sub-therapeutic mannitol)</b>   |  |  |
| CF-301   | Clinical Study Report DPM-CD-301. Long term administration of inhaled dry powder mannitol in cystic fibrosis - A safety and efficacy study.  | 2012.  |
| CF-301 open label  | Abbreviated Clinical Study Report DPM-CF-301 open label phase. . Long term administration of inhaled dry powder mannitol in cystic fibrosis - A safety and efficacy study (open label phase).<br><br>Bilton, D., Robinson, P., Cooper, P., Gallagher, C. G., Kolbe, J., Fox, H., Jaques, A., and Charlton, B. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study   | 2012.<br><br>European Respiratory Journal 2011; 38: 1071-1080.                                 |
| CF-302   | Clinical Study Report DPM-CF-302. Long term administration of inhaled mannitol in cystic fibrosis- A safety and efficacy study.  | 2012.  |
| CF-302 open label  | Abbreviated Clinical Study Report DPM-CF-302 Open Label Phase. Long term administration of inhaled mannitol in cystic fibrosis- A safety and efficacy study (open label phase).<br><br>Aitken, M. L., Bellon, G., de Boeck, K., Flume, P. A., Fox, H. G., Geller, D. E., Haarman, E. G., Hebestreit, H. U., Lapey, A., Schou, I. M., Zuckerman, J. B., and Charlton, B. Long-term inhaled dry powder mannitol in cystic fibrosis: An international randomized study. | 2012.<br><br>American Journal of Respiratory and Critical Care Medicine 2012; 185(6): 645-652. |
| IIS-B-118  | Middleton, A., Robinson, P. D., McKay, K., Jaffe, A. and Selvadurai, H. A pilot study of inhaled dry-powder mannitol during cystic fibrosis-related pulmonary exacerbation.  | European Respiratory Journal 2015; 45: 541-544.  |
| <b>mannitol versus placebo (non-respirable mannitol)</b> |  |  |
| CF-201   | DPM-CF-201. A phase 2 study to determine the safety and efficacy of inhaled dry powder mannitol in cystic fibrosis.<br><br>Jaques, A., Daviskas, E., Turton, J. McKay, K., Cooper, P., Stirling, R. G., Robertson, C. F., Bye, P. T., LeSouef, P. N., Shadbolt, B., Anderson, S. D., and Charlton, B. Inhaled mannitol improves lung function in cystic fibrosis.  | 2012.<br><br>Chest 2008; 133: 1388-1396.   |
| CF-204   | Clinical Study Report DPM-CF-204. A randomised, multicentre, double-blind, placebo-controlled, crossover trial determining the efficacy of dry powder mannitol in improving lung function in subjects with cystic fibrosis aged six to seventeen years.  | 2016.  |

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| Trial ID   | Protocol title/ Publication title  | Publication citation                             |
|--|--|--|
|  | De Boeck, K., Haarman, E., Hull, J., Lands, L. C., Moeller, A., Munck, A., Riethmuller, J., Tiddens, H., Volpi, S., Leadbetter, J., Charlton, B., and Malfroot, A. Inhaled dry powder mannitol in children with cystic fibrosis: A randomised efficacy and safety trial.   | Journal of Cystic Fibrosis 2017; 16(3): 380-387. |
| <b>mannitol vs. DNase vs. mannitol/DNase combination</b> |  |  |
| CF-203   | Pharmaxis trial report. DPM-CF-203. A cross-over comparative study of inhaled mannitol, alone and in combination with daily rhDNase, in children with cystic fibrosis.<br><br>Minasian, C., Wallis, C., Metcalfe, C., and Bush, A. Comparison of inhaled mannitol, daily rhDNase and a combination of both in children with cystic fibrosis: A randomised trial. | 2012.<br><br>Thorax 2010; 65: 51-56.             |

Source: Table B.2.3, pp62-63 of the resubmission

6.7 The key features of the randomised trials are summarised in Table 4. Trial CF-203 and IIS-B-118 (which were inappropriately excluded by the resubmission) were included during the evaluation.

**Table 4: Key features of the evidence included in the submission and evaluation**

| Trial  | N   | Design/ duration  | Risk of bias | Patient population   | Outcomes                          | Use in modelled evaluation   |
|--|-----|---|--------------|--|-----------------------------------|--|
| <b>mannitol versus control (low dose mannitol)</b>       |     |   |              |  |                                   |  |
| CF-301   | 295 | R, DB, MC<br>26 wks   | Low          | >6yrs;<br>55% DNase users  | Spirometry <sup>c</sup> ;<br>PDPE | % predicted FEV <sub>1</sub> (wk 26), response <sup>a</sup> , exacerbations <sup>b</sup> |
| CF-302   | 305 | R, DB, MC<br>26 wks   | Low          | >6yrs;<br>75% DNase users  |                                   |  |
| Meta-analysis  | 600 | Included CF-301 and CF-302; sub-group analysis by DNase use |              |  |                                   |  |
| IIS-B-118 (Middleton 2015)                               | 22  | R, DB, MC<br>12 days  | High         | >6yrs; hospitalised with acute pulmonary exacerbation treated with IV antibiotics; 59% DNase users | Spirometry <sup>c</sup>           | Not used   |
| <b>mannitol versus placebo (non-respirable mannitol)</b> |     |   |              |  |                                   |  |
| CF-201   | 39  | R, DB, MC, 2A<br>crossover<br>2 wks                         | Low          | >8 yrs;<br>46% DNase users   | Spirometry <sup>c</sup>           | Not used   |
| CF-204   | 95  | R, DB, MC, 2A<br>crossover<br>8wks                          | Low          | 6-18 yrs;<br>69% DNase users   | Spirometry <sup>c</sup>           | Not used   |
| <b>mannitol + DNase versus DNase</b>                     |     |   |              |  |                                   |  |
| CF-203   | 26  | R, OL,MC, 3A<br>crossover<br>12 wks                         | High         | 8-19 yrs;<br>89% DNase users   | Spirometry <sup>c</sup> ;<br>PDPE | Not used   |

Abbreviations: DB=double blind; DNase=dornase alfa; MC=multicentre, OL=open-label; PDPE=protocol defined pulmonary exacerbations; R=randomised; 2A=2-arm; 3A=3-arm, N=number analysed.

Source: compiled during the evaluation

<sup>a</sup> Model uses response rates derived from data on patients with no changes from baseline in ppFEV<sub>1</sub> at 14 weeks.

<sup>b</sup> Those patients who continue to remain in the 'mannitol responders' group experience a reduction in their rate of exacerbations.

<sup>c</sup> Reported spirometry outcomes include forced expiratory volume over one second (FEV<sub>1</sub>), forced vital capacity (FVC), FEV<sub>1</sub>/FVC, forced expiratory flow 25-75% in middle half of an expiration (FEF<sub>25-75</sub>), peak expiratory flow (PEF).

## Comparative effectiveness

6.8 The results for Trials CF-301, CF-302 and CF-203 were previously presented in the March 2011 submission and remain unchanged. Table 5 summarises the main spirometry outcomes (absolute and relative changes in FEV<sub>1</sub> from baseline) reported for Trials CF-301, CF-302, CF-201 and CF-203.

**Table 5: Results of absolute and relative change in FEV1 from baseline across the randomised trials**

| Trials  | Absolute change from baseline (mL) (95% CI) |                                     |   | Relative % change from baseline (mL) (95% CI) |                                 |   |
|---|---|-------------------------------------|---|---|---------------------------------|---|
|   | mannitol 400mg BD <sup>#</sup>              | Comparator                          | Difference Mannitol vs. comparator              | mannitol 400mg BD <sup>#</sup>                | Comparator                      | Difference Mannitol vs. comparator            |
| <b>Mannitol + DNase versus DNase alone</b>                          |   |                                     |   |   |                                 |   |
| CF-203 (N=26 <sup>^</sup> )   | 9mL<br>(SD=0.30)                            | 105mL<br>(SD=0.22)                  | -96mL<br>p=0.1337                               | -0.77%***<br>(SD=17.53)                       | 9.07 %<br>(SD=17.67)            | -9.84%<br>(-20.25, 0.57)                      |
| <b>Mannitol versus placebo (phase 2 trials)</b>                     |   |                                     |   |   |                                 |   |
| CF-201 <sup>#</sup> (N=39)  | 120.3 mL<br>(56.6, 184.0)                   | 1.0mL<br>(-64.4, 66.3)              | <b>119.3mL<br/>(29.3, 209.4)<br/>p&lt;0.05</b>  | 6.97*<br>(3.44, 10.50)                        | 0.30<br>(-3.31, 3.92)           | <b>6.67<br/>(1.98, 11.35)<br/>(p&lt;0.01)</b> |
| Subgroup results from CF-201  |   |                                     |   |   |                                 |   |
| DNase users (N=18)  | -   | -                                   | -   | 5.42*<br>(SD=12.54)                           | 0.08<br>(SD=8.98)               | 5.34 <sup>b</sup><br>(-1.79, 12.47)           |
| DNase non-users (N=21)  | -   | -                                   | -   | 8.35*<br>(SD=14.02)                           | 0.22<br>(SD=7.74)               | <b>8.13<sup>b</sup><br/>(1.28, 14.98)</b>     |
| <b>Mannitol versus control (50 mg BD mannitol) (phase 3 trials)</b> |   |                                     |   |   |                                 |   |
| CF-301 (N=295)  | 121.35mL (89.2, 153.5)<br>p<0.001           | 26.9mL<br>(-10.2, 63.9)<br>p=0.154  | <b>94.45mL<br/>(46.2, 142.7)<br/>p&lt;0.001</b> | 6.32%**<br>(4.6, 8.1)<br>p<0.001              | 2.42%<br>(0.4, 4.4)<br>p=0.018  | <b>3.91%<br/>(1.31, 6.50)<br/>p=0.003</b>     |
| CF-302 (N=305)  | 106.53 mL (62.4, 150.6) p<0.001             | 52.38mL<br>(2.1, 102.7)<br>p=0.041  | 54.14mL<br>(-2.0, 110.3)<br>p=0.059             | 8.22%**<br>(5.6, 10.9)<br>p<0.001             | 4.47%<br>(1.4, 7.5)<br>p=0.004  | <b>3.75%<br/>(0.38, 7.12)<br/>p=0.0291</b>    |
| Pooled CF-301/302   | 114.05 mL (87.2, 140.9)<br>p<0.001          | 40.63mL<br>(9.9, 71.4)<br>p=0.01    | <b>73.42mL<br/>(36.2, 110.7)<br/>p&lt;0.001</b> | 7.32%<br>(5.8, 8.9)<br>p<0.001                | 3.52%<br>(1.7, 5.3)<br>p<0.001  | <b>3.80%<br/>(1.64, 5.96)<br/>p&lt;0.001</b>  |
| Subgroups of the combined CF-301/302 populations                    |   |                                     |   |   |                                 |   |
| DNase users (N=392)   | 79.38mL (46.6, 112.2)<br>p<0.001            | 22.65mL<br>(-14.6, 60.0)<br>p=0.233 | <b>56.73mL<br/>(12.1, 101.4)<br/>p=0.013</b>    | 5.34%<br>(3.4, 7.3)<br>p<0.001                | 2.21%<br>(0.01, 4.4)<br>p=0.049 | <b>3.14%<br/>(0.50, 5.78)<br/>p=0.02</b>      |
| DNase non-users (N=208)   | 150.98mL<br>(109.9, 192.1)<br>p<0.001       | 54.49mL<br>(5.9, 103.1)<br>p=0.028  | <b>96.50mL<br/>(34.9, 158.1)<br/>p=0.002</b>    | 9.44%<br>(7.0, 11.9)<br>p<0.001               | 4.57%<br>(1.7, 7.4)<br>p=0.002  | <b>4.88%<br/>(1.24, 8.51)<br/>p=0.009</b>     |

Abbreviations: N=number analysed, DNase=dornase alfa, BD=twice daily

Shaded cells represent the comparisons of interest of mannitol + DNase versus DNase alone.

Note: CF-301a refers to re-run of analyses without baseline (i.e. week 6-26) – refer p90 of the resubmission. The minimum FEV<sub>1</sub> inclusion threshold was higher in CF-302 (≥40% predicted versus ≥30% in CF-301). To enable integration (pooling) and direct comparison of the two studies, a common approach was employed, using the data derivation conventions and analysis models defined in the Statistical Analysis Plan for CF-302.

<sup>#</sup> Trial CF-201 used a Mannitol dose of 420mg BD which is outside the TGA-approved dose of 400mg BD

<sup>^</sup> Number analysed as per the trial report for CF-203, which conflicts with the main publication for CF-203 by Minasian 2010.

\*CF-201: 2 weeks;

\*\* CF-301a/CF-302: 26 weeks, Mixed effect Model Repeated Measurement (MMRM);

\*\*\* CF-203: 12 weeks, generalized linear mixed model analysis.

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Source: Table B.6.1, B.6.9, Table C.3.1; pp.108-120, 171 of resubmission; Attachment 7.C3.1.T; Table 11.4.2.1, p56 of CSR for CF-201; Table 11.4.1.1, 11.4.1.3, pp.56-57 of CSR for CF-203 and calculated during the evaluation in RevMan 5.1.

- 6.9 Mannitol was associated with statistically significant improvements in FEV<sub>1</sub> compared with placebo/control in the overall populations of Trials CF-301, CF-302, and CF-201. However, although the results favoured mannitol for Trial CF-302, the difference in absolute change in FEV<sub>1</sub> was not statistically significant versus control treatment with low dose mannitol (54.14mL, 95% CI: -2.0, 110.3 p=0.059).
- 6.10 In the population most representative of the requested PBS population (i.e. DNase users, represented by shaded cells in Table 5), the treatment effect of mannitol varied. In Trials CF-301/302, mannitol treatment was associated with statistically significant improvements in FEV<sub>1</sub> outcomes compared with control in the DNase users subgroup. However, this contrasted with the result of Trial CF-203, and the subgroup of DNase users in Trial CF-201, where there were no statistically significant differences in FEV<sub>1</sub> outcomes for patients who added on mannitol to DNase (although the number of patients contributing results were small: 18 in Trial CF-201 and 26 in Trial CF-203). The ESC noted that in Trial CF-203, the combination of mannitol and DNase showed no change from baseline to endpoint in mean change in FEV<sub>1</sub> and appeared to perform worse than either treatment administered separately (although these differences were not statistically significant).
- 6.11 The results for the open-label phases in Trials CF-301 and CF-302 indicated that the treatment benefit of mannitol was maintained over 52 weeks, and over 78 weeks for a small number of patients (n=36). In Trial CF-302, the open label phase ended at 52 weeks. For Trial CF-301, only a small number of subjects were available for analysis at Week 78 (17 and 36 in the control and mannitol groups, respectively).
- 6.12 Table 6 illustrates the results for pulmonary exacerbations and hospitalisations reported in Trials CF-301 and CF-302. Table 7 summarises the proportion of patients with PDPE in Trial CF-203.

**Table 6: Pulmonary exacerbations and hospitalisations reported in the mannitol vs. control trials (CF-301, CF-302) – ITT Population and DNase user and non-user subgroups**

| Trial ID  | Mannitol                       | Control                        | Rate Ratio (unless otherwise specified) (95% CI)   |
|---|--------------------------------|--------------------------------|--|
| <b>Mean annualised rate of PDPE events per patient (resubmission derived)</b> |                                |                                |  |
| CF-301  | 0.78 (SD: 1.98) n=177          | 1.05 (SD 2.15) n= 118          | 0.77 (0.50, 1.18)                                  |
| CF-302  | 0.44 (95% CI 0.31, 0.60) n=184 | 0.50 (95% CI 0.35, 0.72) n=121 | 1.00 (0.61, 1.64) <sup>^</sup>                     |
| <b>Meta-analysis</b>  | 0.5*                           | 0.67*                          | 0.88 (0.63, 1.22) <sup>^</sup>                     |
| <b>Mean annualised rate of PDPE events per patient (evaluation derived)</b>   |                                |                                |  |
| CF-301  | 0.78 (SD 1.98) n=177           | 1.05 (SD 2.15) n=118           | 0.74 (0.47, 1.18)                                  |
| CF-302  | 0.44 (95% CI 0.31, 0.60) n=184 | 0.50 (95% CI 0.35, 0.72) n=121 | 0.85 (0.51, 1.41)                                  |
| <b>Meta-analysis</b>  | 0.5*                           | 0.67*                          | 0.79 (0.56, 1.11)                                  |
| <b>-Sub-group results from Trials CF-301 and CF-302</b>                       |                                |                                |  |
| -CF-301 DNase users   | 1.05 (SD 2.29) n=97            | 1.19 (SD 2.30) n=65            | 0.76 (0.45, 1.27) p>0.05                           |
| -CF-302 DNase users   | 0.53 (95% CI 0.37, 0.75) n=136 | 0.43 (95% CI 0.27, 0.67) n=93  | 1.09 (0.61, 1.95) p=0.779                          |
| <b>Meta-analysis of results (DNase users)</b>                                 |                                |                                | 0.89 (0.61, 1.31)                                  |
| -CF-301 DNase non-users   | 0.47 (SD 1.48) n=80            | 0.86 (SD 1.93) n=53            | 0.59 (0.24, 1.47) p>0.05                           |
| -CF-302 DNase non-users   | 0.18 (95% CI 0.07, 0.49) n=48  | 0.74 (95% CI 0.40, 1.37) n=28  | 0.34 (0.10, 1.09) p=0.069                          |
| <b>Meta-analysis of results (DNase non-users)</b>                             |                                |                                | <b>0.48 (0.23, 0.99)</b>                           |
| <b>Incidence of PDPE events</b>   |                                |                                |  |
| CF-301  | 32/177 (18.1%)                 | 33/118 (28.3%)                 | RD: -9.8% (-20, 0)<br>RR: <b>0.65 (0.42, 0.99)</b> |
| CF-302  | 28/184 (15.2%)                 | 23/121 (19%)                   | RD: -3.8% (-12, 5)<br>RR: 0.80 (0.48, 1.32)        |
| <b>Meta-analysis</b>  | 60/361 (16.6%)                 | 56/239 (23.4%)                 | RD: -6.8% (-13, 0)<br>RR: <b>0.71 (0.51, 0.98)</b> |
| <b>Mean annualised rate of PE events per patient</b>                          |                                |                                |  |
| CF-301  | 1.61 (SD 2.80) n=177           | 1.89 (SD 2.52) n=118           | 0.86 (0.64, 1.17)                                  |
| CF-302  | 2.08 (95% CI 1.79, 2.42)       | 2.20 (95% CI 1.85, 2.62)       | 0.93 (0.74, 1.17)                                  |
| <b>Meta-analysis</b>  |                                |                                | 0.90 (0.75, 1.08)                                  |
| <b>-Sub-group results from Trials CF-301 and CF-302</b>                       |                                |                                |  |
| -CF-301 DNase users   | 1.82 (SD 2.80)                 | 2.18 (SD 2.75)                 | 0.76 (0.55, 1.06) p>0.05                           |
| -CF-302 DNase users   | 2.36 (95% CI 2.00, 2.78)       | 2.20 (95% CI 1.80, 2.68)       | 1.00 (0.77, 1.30) p=0.977                          |
| <b>Meta-analysis (DNase users)</b>  |                                |                                | 0.90 (0.73, 1.10)                                  |
| -CF-301 DNase non-users   | 1.37 (SD 2.79)                 | 1.51 (SD 2.16)                 | 0.94 (0.55, 1.56) p>0.05                           |
| -CF-302 DNase non-users   | 1.33 (95% CI 0.92, 1.91)       | 2.22 (95% CI 1.55, 3.17)       | 0.69 (0.41, 1.16) p=0.162                          |
| <b>Meta-analysis (DNase non-users)</b>  |                                |                                | 0.80 (0.55, 1.16)                                  |
| <b>Rate of rescue antibiotic use for PE</b>                                   |                                |                                |  |
| CF-301  | NR                             | NR                             | 0.73 (0.39, 1.37)                                  |
| CF-302  | NR                             | NR                             | 0.91 (0.78, 1.07)                                  |
| <b>Meta-analysis</b>  |                                |                                | 0.90 (0.77, 1.05)                                  |
| <b>Rate of hospitalisation for PE</b>   |                                |                                |  |
| CF-301  | NR                             | NR                             | 0.88 (0.32, 2.39)                                  |
| CF-302  | NR                             | NR                             | 0.75 (0.45, 1.23)                                  |
| <b>Meta-analysis</b>  |                                |                                | 0.77 (0.49, 1.21)                                  |
| <b>% hospitalised due to PDPE</b>   |                                |                                |  |
| CF-301  | 24/177 (13.6)                  | 20/118 (16.9)                  | RR: 0.80 (0.46, 1.38)                              |
| CF-302  | 22/184 (12.0)                  | 19/121 (15.7)                  | RR: 0.76 (0.43, 1.35)                              |
| <b>Meta-analysis</b>  |                                |                                | RR: 0.78 (0.53, 1.16)                              |

Abbreviations: CI, confidence interval; NR, not reported; PDPE, protocol defined pulmonary exacerbation; PE, pulmonary exacerbation; RR; relative risk; RD: risk difference; SD, standard deviation. RD=risk difference  
 Shaded cells represent the comparisons of interest of mannitol + DNase versus DNase alone. \* Raw rate = total number of events/total follow up time. <sup>^</sup>as per integrated Studies Appendix Table pd01ana3\_201.pdf.

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Source: Table B.6.14; B.6.18; pp.129-134 of re-submission; pp.83, 98 of CSR for CF-301; pp.88, 101 of CSR for CF-302, and calculated during the evaluation using RevMan 5.1.

**Table 7: Proportion (%) of patients with PDPE# in Trial CF-203**

| Outcomes                | DNase<br>(N = 21) | mannitol with DNase<br>(N = 23) | Difference |
|-------------------------|-------------------|---------------------------------|------------|
| % of patients with PDPE | 3 (14.3)          | 6 (26.1)                        | p=0.2568   |

Abbreviation: PDPE, protocol defined pulmonary exacerbation. # PDPE was determined by the use of IV antibiotics, but the presence of other signs/symptoms were not stated.

Source: Extracted during evaluation from Table 11.4.1.20, p77 of trial report for CF-203

- 6.13 There were no consistent statistically significant differences in exacerbation rates or hospitalisations between mannitol and control in the ITT populations in Trials CF-301 or CF-302. However, the results just reached statistical significance for incidence of protocol defined pulmonary exacerbation (PDPE) events when results of CF-301 and CF-302 were pooled for mannitol versus control (RR: 0.71 95% CI: 0.51, 0.98). There was no statistically significant difference in pulmonary exacerbation rates between mannitol and control in the sub-groups of patients on DNase. In Trial CF-203, while there were no statistically significant differences in the proportion of patients with PDPE events between treatment groups, a higher proportion of patients had PDPE events on mannitol + DNase compared to DNase alone (26.1% versus 14.3%).
- 6.14 Trials CF-301/302 reported quality of life outcomes using the revised cystic fibrosis questionnaire (CFQ-R) for the total trial populations. The evaluation also included the CFQ-R (respiratory domain) subscores for the total population in the excluded trial, CF-203. There were some statistically significant differences in quality of life subscores between mannitol and control, for the physical and vitality domains of the CFQ-R, for Trial CF-301. However, there were no significant differences in quality of life scores between mannitol and control in Trial CF-302 in any of the reported domains (respiratory, physical or vitality). In Trial CF-203 there were no statistically significant differences in respiratory quality of life scores between treatment groups; however, the results had favoured the DNase alone treatment group versus combination therapy of mannitol + DNase.

**Comparative harms**

- 6.15 The safety results for Trials CF-301, CF-302 and CF-203 remain unchanged from previous submissions. Although similar proportions of patients treated with mannitol and control experienced adverse events (AEs), treatment-related AEs and associated trial discontinuations were reported for a greater percentage of subjects on mannitol versus control/placebo and this difference was statistically significant in Trial CF-301. In Trial CF-203, there were no significant differences between mannitol + DNase and DNase only groups with respect to either treatment-related AEs or severe AEs. The safety results from the Phase II trials (CF-201 and CF-204) showed a consistent pattern with that of the other trials.
- 6.16 Patients were more likely to experience cough, haemoptysis and pharyngolaryngeal pain with mannitol compared with control. The difference between the proportion

of patients with pharyngolaryngeal pain also reached statistical significance in Trial CF-301 (relative risk: 3.20, 95% CI: 1.26, 8.15).

- 6.17 In the open-label extension phases of Trials CF-301 and CF-302, there were no notable increases in the frequencies of AEs, leading to discontinuation during the open-label phases compared to those reported during the 26-week double-blind phase.
- 6.18 Additional data on potential safety concerns beyond those identified in the clinical trials found no specific new safety issues outside those already identified in the previous submissions for mannitol.

***Benefits/harms***

- 6.19 A summary of the comparative benefits and harms for mannitol versus control is presented in Table 8.

**Table 8: Summary of comparative benefits and harms for mannitol and control**

| <b>Continuous Outcome I: absolute change in FEV<sub>1</sub> from baseline (mL)</b>                 |            |   |                          |                          |   |                          |   |
|--|------------|---|--------------------------|--------------------------|---|--------------------------|---|
|  | mannitol   |   |                          | control                  |   |                          | Mean difference*:<br>mannitol vs. control<br>(95% CI) |
|  | n          | Mean Δ<br>FEV <sub>1</sub> (mls)                | SD<br>(95%CI)            | n                        | Mean Δ<br>FEV <sub>1</sub> (mls)                | SD<br>(95%CI)            |   |
| <b>Mannitol + DNase versus DNase alone</b>   |            |   |                          |                          |   |                          |   |
| CF-203   | 23         | 9   | 0.30                     | 21                       | 105   | 0.22                     | -96mL (-250, 60)                                      |
| <b>Mannitol versus control (50 mg BD mannitol) (phase 3 trials)</b>                                |            |   |                          |                          |   |                          |   |
| Pooled CF-301/302  | 361        | 114.05  | (87.2, 140.9)            | 239                      | 40.63   | (9.9, 71.4)              | <b>73.42mL (36.2, 110.7)</b><br>p<0.001               |
| DNase users  | 233        | 79.38   | (46.6, 112.2)            | 158                      | 22.65   | (-14.6, 60)              | <b>56.73mL (12.1, 101.4)</b><br>p=0.013               |
| DNase non users  | 128        | 150.98  | (109.9, 192.1)           | 81                       | 54.49   | (5.9, 103.1)             | <b>96.50mL (34.9, 158.1)</b><br>p=0.002               |
| <b>Continuous Outcome II: Mean annualised rate of PDPE events per patient (evaluation derived)</b> |            |   |                          |                          |   |                          |   |
|  | mannitol   |   |                          | control                  |   |                          | Rate Ratio*:<br>mannitol vs. control<br>(95% CI)      |
|  | n          | Mean rate<br>of PDPE<br>(events per<br>patient) | SD<br>(95%CI)            | n                        | Mean rate<br>of PDPE<br>(events per<br>patient) | SD<br>(95%CI)            |   |
| CF-301   | 177        | 0.78  | 1.98                     | 118                      | 1.05  | 2.15                     | 0.74 (0.47, 1.18)                                     |
| CF-302   | 184        | 0.44  | (0.31, 0.60)             | 121                      | 0.50  | (0.35, 0.72)             | 0.85 (0.51, 1.41)                                     |
| <b>pooled</b>  | <b>361</b> | <b>0.50</b>                                     | <b>-</b>                 | <b>239</b>               | <b>0.67</b>                                     | <b>-</b>                 | <b>0.79 (0.56, 1.11)</b>                              |
| -CF-301 DNase users  | 97         | 1.05  | 2.29                     | 65                       | 1.19  | 2.30                     | 0.76 (0.45, 1.27)                                     |
| -CF-302 DNase users  | 136        | 0.53  | (0.37, 0.75)             | 93                       | 0.43  | (0.27, 0.67)             | 1.09 (0.61, 1.95)                                     |
| <b>Pooled DNase users</b>  |            |   |                          |                          |   |                          | <b>0.89 (0.61, 1.31)</b>                              |
| -CF-301 DNase non users  | 80         | 0.47  | 1.48                     | 53                       | 0.86  | 1.93                     | 0.59 (0.24, 1.47)                                     |
| -CF-302 DNase non users  | 48         | 0.18  | (0.07, 0.49)             | 28                       | 0.74  | (0.40, 1.37)             | 0.34 (0.10, 1.09)                                     |
| <b>Pooled DNase non users</b>  |            |   |                          |                          |   |                          | <b>0.48 (0.23, 0.99)</b>                              |
| <b>Harms</b>   |            |   |                          |                          |   |                          |   |
| <b>Treatment-related AE</b>  |            |   |                          |                          |   |                          |   |
|  | Mannitol   | control/<br>PBO                                 | RR<br>(95% CI)           | Event rate/100 patients* |   | RD<br>(95% CI)           |   |
|  |            |   |                          | mannitol                 | control/PBO                                     |                          |   |
| CF-301   | 72/177     | 26/118  | <b>1.85 (1.26, 2.71)</b> | 40.7                     | 22.0  | <b>0.19 (0.08, 0.29)</b> |   |
| CF-302   | 44/184     | 21/121  | 1.38 (0.86, 2.20)        | 23.9                     | 17.4  | 0.07 (-0.03, 0.16)       |   |
| CF-201   | 27/38      | 25/36   | 1.02 (0.76, 1.38)        | 71.1                     | 69.4  | 0.02 (-0.19, 0.22)       |   |
| CF-203   | 17/23      | 17/21   | 0.91 (0.66, 1.26)        | 73.9                     | 81.0  | -0.07 (-0.32, 0.18)      |   |
| CF-204   | 15/87      | 10/87   | 1.50 (0.71, 3.15)        | 17.2                     | 11.5  | 0.06 (-0.05, 0.16)       |   |

Abbreviations: AE=adverse events; PBO=placebo; PDPE = protocol-defined pulmonary exacerbation; RD = risk difference; RR = risk ratio; SD=standard deviation.

\* Median duration (range) of exposure: CF-301 = 175 (1-231) days; CF-302= 183 (0-210); CF-201 not reported, CF-203 = 170 (16-198); CF-204 = 56 (1-77).

Source: Tables B.6.1, B.6.21, C.3.1, pp.108-171 of the resubmission, Table 12.2.1.1, p59 of CSR for CF-201; Table 28, p70 of CSR for CF-204; Table 12.3.1, p85 of CSR for CF-203 and calculated during the evaluation.

6.20 On the basis of direct evidence presented by the resubmission, the comparison of mannitol + BSC and control + BSC over a median follow-up of approximately 26 weeks in CF-301/302 resulted in:

- Approximately 73mL improvement in lung function (absolute change in FEV<sub>1</sub>).

- Approximately 7 (CF-302) or 19 (CF-301) additional patients with a treatment related adverse event for every 100 patients treated, most commonly cough, haemoptysis and pharyngolaryngeal pain.
- In the subgroup of patients who were DNase users (of relevance to the current resubmission), there was no significant difference in the prevalence of pulmonary exacerbations between mannitol and control. Amongst the subgroup who were not DNase users, the prevalence of pulmonary exacerbation events was approximately halved with use of mannitol vs control.

### ***Clinical claim***

6.21 The resubmission described mannitol + BSC (which may or may not include DNase) as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo/control + BSC (which may or may not include DNase). The claim was appropriate with respect to safety. However, the ESC considered the claim was inadequately supported with respect to effectiveness as the evidence did not directly inform the requested additional population of patients who are inadequately responsive to DNase and seek to add mannitol to existing DNase therapy because:

- None of the included trials had specifically enrolled patients who were inadequately responsive to DNase; the closest proxy was patients who were taking concomitant DNase in the trials (Trial CF-203 and subgroups of patients in Trials CF-201, CF-301 and CF-302).
- Trial CF-203, which directly compared patients taking concomitant DNase and mannitol and the two therapies separately, found no significant differences in lung function between mannitol + DNase versus DNase. The FEV<sub>1</sub> results showed combined use to be numerically worse than DNase alone, although the difference was not statistically significant.
- For the sub-group of 18 patients using DNase in Trial CF-201, no significant difference between mannitol and placebo was found in percentage change in FEV<sub>1</sub> from baseline.
- For Trials CF-301 and CF-302, the incremental benefits with respect to both the statistically significant FEV<sub>1</sub> outcomes and the non-significant clinical outcomes were consistently smaller in the DNase users subgroups than the ITT populations which included 34.7% of patients who were not taking concurrent DNase.
- Despite some statistically significant differences in FEV<sub>1</sub> outcomes, there were no significant differences between mannitol and control treatments in mean annualised rate of PDPE events per patient or hospitalisation in CF-301/302 for either the ITT population or DNase user subgroup. In Trial CF-203, there were no statistically significant differences in the proportion of patients with PDPE events

between treatment groups. A higher proportion of patients had PDPE events on mannitol + DNase compared with DNase alone (although this difference did not reach statistical significance).

- 6.22 The PSCR (p1-2) argued that concomitant DNase use was not a statistically significant treatment effect modifier, and thus, use of the ITT population as the basis for the effectiveness claim was appropriate. The ESC considered that the ITT population from CF-301/302 was not relevant to the requested expansion to the PBS population. The ESC agreed that DNase use was not demonstrated to be a treatment effect modifier, but questioned whether the interaction analysis was adequately powered. The ESC further noted that the treatment effect for mannitol versus control was consistently smaller for the subgroup that was also being treated with DNase across all the spirometry outcomes.
- 6.23 The PSCR (p2) noted that as a number of disparate studies were included in the submission, FEV<sub>1</sub> was the unifying endpoint across the studies and FEV<sub>1</sub> is linked to mortality, so any significant difference between placebo and treatment is potentially clinically relevant. The PSCR argued that due to the relative infrequency of pulmonary exacerbations, they represent a difficult endpoint for clinical trials in CF. Nevertheless, the ESC noted there were generally a lack of significant differences between mannitol and control treatments in relation to mean annualised rate of PDPE events per patient or hospitalisations due to exacerbations, for either the ITT population or the subgroup of patients receiving concurrent DNase.
- 6.24 The PBAC considered that the claim that mannitol + BSC (which may or may not include DNase) is superior in terms of comparative effectiveness over placebo/control + BSC (which may or may not include DNase) was reasonable. However, the PBAC agreed with the ESC that this comparison and the evidence presented in the submission did not inform the requested additional population of patients who are inadequately responsive to DNase and seek to add mannitol to existing DNase therapy. Nevertheless, the PBAC considered that there is likely to be a small group of patients who would benefit from combination therapy compared with DNase monotherapy.
- 6.25 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.26 The modelled economic evaluation was updated compared with the March 2011 submission. While the overall structure of the model was similar, the model no longer included change in respiratory symptoms as distinct from ppFEV<sub>1</sub> or their associated differences in utilities. Resource data were also no longer sourced from the trials. The patient population used in the model was based on the combined ITT populations from Trial CF-301/CF-302. The type of economic evaluation presented was a cost-utility analysis comparing the incremental costs and benefits of using

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mannitol + BSC, versus BSC alone (where BSC may or may not include DNase). The model assumed that 65% of patients were receiving concomitant treatment with DNase.

6.27 The ESC considered that the model did not provide a reliable indication of the cost-effectiveness of the comparison relevant to the requested change to the current listing; i.e. mannitol + DNase, compared with optimised DNase + placebo.

**Table 9: Summary of model structure and rationale**

| Component                        | Summary  |
|----------------------------------|--|
| Time horizon                     | 100 years (lifetime) in the model base case versus 74 weeks in trials  |
| Outcomes                         | LYs and QALYs gained   |
| Methods used to generate results | <p>Patient-level simulation Markov model (10,000 patients/trials). Patient characteristics (including gender, age, BMI, ppFEV<sub>1</sub>, Burkholderia cepacia complex (Bcc) infection status and ppFEV<sub>1</sub> responder at Week 14) were sampled at baseline and influenced patient transitions through the model (see 'Transition probabilities' below). All patients commenced in a base CF health state. Each cycle, patients with ppFEV<sub>1</sub> &lt;30 have a chance to receive a lung transplant. Patients who did not receive a lung transplant remain at risk of experiencing a pulmonary exacerbation in that cycle, dying due to CF or dying due to an unrelated cause. Patients who did receive a lung transplant were no longer at risk of suffering pulmonary exacerbations and remained in that health state until death (due to CF or an unrelated cause).</p> <p>In the mannitol arm of the model, all patients were assumed to commence on mannitol. Patients classified as mannitol week 14 'responders' at baseline ceased therapy at a constant rate from the first cycle; whereas all patients classified as non-responders cease therapy after the first cycle. However responders who ceased in cycles 0, 1 and 2 were still attributed a response at Week 26.</p>  |
| Health states                    | 1) CF; 2) Lung transplant; 3) Dead   |
| Utilities                        | CF ppFEV <sub>1</sub> ≥30: 0.92; CF ppFEV <sub>1</sub> <30: 0.31; Lung transplant: 0.803; Exacerbation: -0.0097 / event  |
| Cycle length                     | 1 <sup>st</sup> cycle and ≥3 <sup>rd</sup> cycles: 12 weeks <sup>a</sup> ; 2 <sup>nd</sup> cycle: 2 weeks <sup>b</sup> . No half cycle correction.   |
| Transition probabilities         | <p>Transitions through the model were dependent on patient characteristics (drawn at baseline and tracked over the model) via a number of regression analyses and other assumptions:</p> <p>Absolute ppFEV<sub>1</sub> at week 26 derived from a linear regression which included covariates treatment with mannitol, 'responder' at baseline, BMI at baseline, ppFEV<sub>1</sub> at baseline, and exacerbations.</p> <p>No change in ppFEV<sub>1</sub> assumed for 'responders' on mannitol for a maximum of 48 weeks.</p> <p>Change in ppFEV<sub>1</sub> after week 26 for non-responders or after week 74 for mannitol responders derived from a linear regression which included covariates: age, age≥30 and current exacerbation.</p> <p>Assumed constant rate of exacerbations with reduced risk on mannitol.</p> <p>Assumed constant rate of lung transplant for patients ppFEV<sub>1</sub> &gt;30.</p> <p>Probability of dying due to CF derived from a cox survival model which included covariates ppFEV<sub>1</sub> and BMI, and assumed increased risk with Bcc and current exacerbation; probability of dying due to lung transplant dependent on time since transplant; probability of dying from other causes derived from national life tables.</p> <p>Assumed all non-responders cease mannitol after cycle 0; assumed constant rate of cessation for responders from cycle 0. Inappropriately, cessation of mannitol was unrelated to ppFEV<sub>1</sub>.</p> |
| Software package                 | <p>Trial-based analysis: Excel 2010.</p> <p>Modelled evaluation: TreeAge 2013 (10,000 iterations in base case; this did not appear to be adequate for stable results. 50,000 iterations increased the ICER by 5%).</p>   |

<sup>a</sup> The modelled evaluation uses response rates from CF-301/CF-302 at week 14 as a proxy for response rates at week 12.

<sup>b</sup> The second cycle is set to 2 weeks such that the sum of the first three cycles (i.e. 12 + 2 + 12) equals 26 weeks (the time point at which FEV<sub>1</sub> is taken from CF-301/CF-302). The FEV<sub>1</sub> regression model from the CF-301/CF-302 trial data is used up to week 26 in the model.

Source: constructed during the evaluation

6.28 The method of analysis was an individual patient microsimulation model. Transitions through the model health states (CF, Lung transplant, and Death) were dependent

on patient characteristics drawn at baseline and tracked throughout the model. Treatment with mannitol was assumed to directly improve ppFEV<sub>1</sub> at the start of the model (Week 26) and indirectly across the model via a reduced risk of pulmonary exacerbation on treatment. The difference in ppFEV<sub>1</sub>, as well as reduced risk of pulmonary exacerbation on mannitol, was translated into fewer lung transplants and a lower risk of death. It was unclear whether the resubmission was double counting some of the benefits of treatment with mannitol, particularly with respect to exacerbations and their separate effects on change in ppFEV<sub>1</sub> and mortality.

- 6.29 A key implicit assumption of the model was that cessation of mannitol was not related to a change in ppFEV<sub>1</sub>, therefore any difference in ppFEV<sub>1</sub> established at the start of the model was preserved over the duration of the model. This assumption resulted in considerable survival benefits being accrued to mannitol.
- 6.30 The ESC considered the utilities used in the model did not adequately reflect the relationship between ppFEV<sub>1</sub> and health-related quality of life. The model used crude utilities for ppFEV<sub>1</sub><30% and ppFEV<sub>1</sub>≥30% (0.92). This means that any direct effect on quality of life of improvement in FEV<sub>1</sub> in the mannitol arm is not captured until a threshold of ppFEV<sub>1</sub>>30% is reached.
- 6.31 The ESC noted that the F1 statutory 5% price cut that will apply to mannitol in April 2018 was applied to the price of mannitol in the economic model. This assumption is contrary to the PBAC Guidelines which state that submissions should value future costs at current prices (PBAC Guidelines, Version 5.0 p.82). However, the ESC did not expect the inclusion of this price change would have a large impact on the estimate of cost effectiveness.
- 6.32 Table 10 provides a summary of the key drivers in the modelled economic evaluation.

**Table 10: Key drivers of the model**

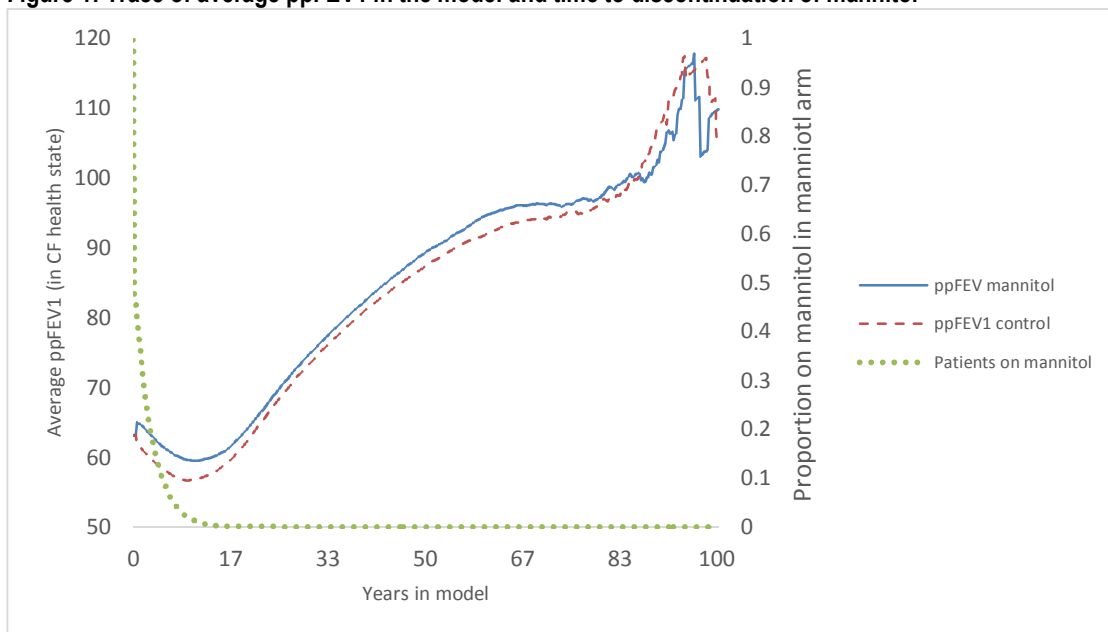
| Description   | Method/Value  | Impact                  |
|---|---|-------------------------|
| Model structural assumption that mannitol cessation was unrelated to changes in ppFEV <sub>1</sub> (the main benefit) | This assumption allowed differences between mannitol and control established by Week 26 were maintained indefinitely in the model regardless of ongoing treatment.  | High, favoured mannitol |
| The assumption that ppFEV <sub>1</sub> increases over time indefinitely for patients over 30 years of age.            | This assumption independently did not drive the model as it was applied to both arms, but together with the inappropriate structural assumption that delinked ongoing treatment and benefits, it allowed that inappropriate difference to be maintained for a lifetime. | High, favoured mannitol |
| Model mortality based on ppFEV <sub>1</sub>   | The model translates the difference in ppFEV <sub>1</sub> from the trials to a considerable difference in survival for a much extended life expectancy, accruing considerable life years over time.   | High, favoured mannitol |

Source: compiled during the evaluation

- 6.33 Figure 1 shows a trace of average ppFEV<sub>1</sub> in the CF health state (left axis) and the proportion of patients on mannitol (right axis), while Figure 2 presents overall survival. The evaluation and the ESC considered that the graphs illustrate four key findings of the model which are not supported by the literature:

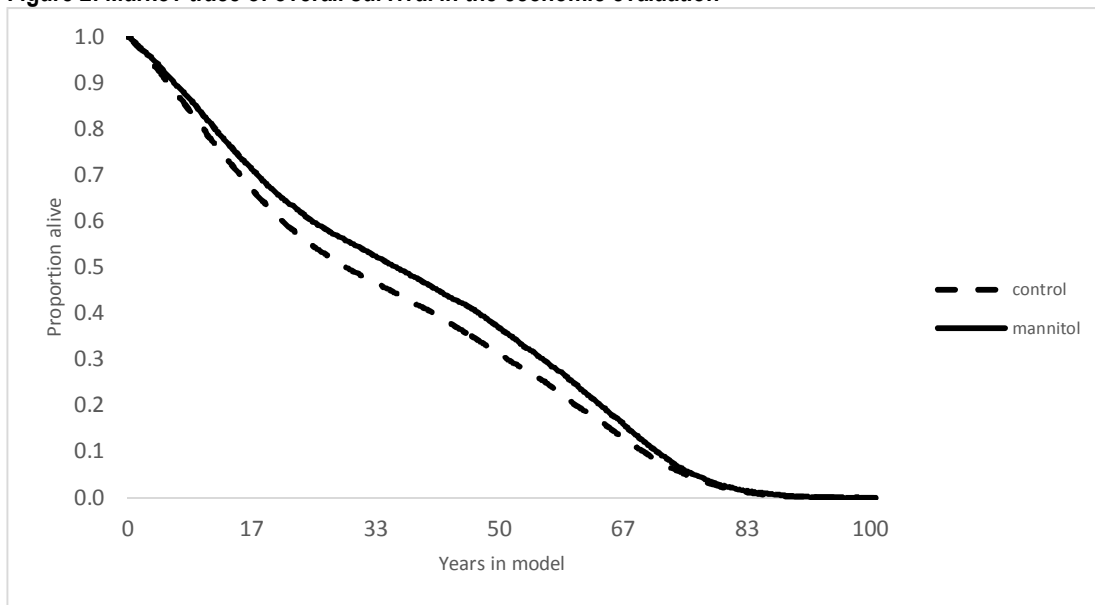
- The model predicted a decrease in ppFEV<sub>1</sub> initially followed by a continuous increase over the age of 30 (at which point almost all patients are no longer receiving mannitol), with 18.93% of patients in the control arm achieving ppFEV<sub>1</sub> >100 within their lifetime. The ESC considered this was implausible, noting that fewer than 10% of patients over the age 20 had ppFEV<sub>1</sub>>100% in Liou et al 2010.
- The difference in ppFEV<sub>1</sub> established between the mannitol and control arms at Week 26 was preserved long after all patients had ceased mannitol.
- A majority of patients are alive after 30 years in the model; the median age at death was 61 years for mannitol versus 52 years for control, compared with median survival of less than 40 years in the literature.
- Discontinuation rates of mannitol were taken from the trial data (CF-301 and CF-302) and applied throughout the model. The ESC considered the discontinuation rate in later cycles was likely to be less than the initial rate, meaning the total use of mannitol in the model is an underestimate.
- A small improvement in ppFEV<sub>1</sub> at Week 26 in the trial data was translated by the model into a considerable survival benefit for mannitol (mean = 3.18 years; median = 6.92 years) in the model. The ESC considered that while there is some evidence supporting a link between ppFEV<sub>1</sub> and survival, it is unlikely to be of this magnitude.

Figure 1: Trace of average ppFEV1 in the model and time to discontinuation of mannitol



Source: constructed during the evaluation

Figure 2: Markov trace of overall survival in the economic evaluation



Source: constructed during the evaluation

6.34 The PSCR (p3-4) acknowledged that the “unusual S-shaped survival curve” was caused by the assumption that ppFEV<sub>1</sub> increases with age over 30 years. The PSCR stated that assuming no change in ppFEV<sub>1</sub> due to age >30 years resulted in reduced median undiscounted survival gain from 6.9 years to 2.8 years, reduced median age of survival in the control arm from 52 to 45 years, and average ppFEV<sub>1</sub> decreased over time. The model was not sensitive to this change in assumption with a small increase in the ICER to \$15,000 - \$45,000 per QALY gained<sup>1</sup> (compared with the base case of \$15,000 - \$45,000 per QALY gained). The ESC considered that this was a more reasonable assumption than that in the submission, but would expect ppFEV<sub>1</sub> would decline with age. Furthermore, the ESC considered this scenario still favoured mannitol (see paragraph 6.34).

6.35 Table 11 provides the results of the stepped economic evaluation.

<sup>1</sup> There were slight discrepancies between the ICERs presented in the PSCR and those conducted during the evaluation (Table 12). The PSCR stated this may be due to different versions of TreeAge.

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**Table 11: Results of the stepped economic evaluation**

| Step and component   | Mannitol + BSC             | Placebo + BSC | Increment                          |
|--|----------------------------|---------------|------------------------------------|
| <b>Step 1a:</b>  |                            |               |                                    |
| - Number of 'responders' at Wk 14 in Trials CF-301/CF-302  |                            |               |                                    |
| - Mannitol drug cost; assuming average treatment duration in Trials CF-301/CF-302 (21 weeks)                               |                            |               |                                    |
| Costs  | \$ [redacted] <sup>a</sup> | \$0           | \$ [redacted]                      |
| 'Responders' Wk 14   | 0.5097                     | 0.4937        | 0.016                              |
| Incremental cost/extra patient responding  |                            |               | \$ [redacted] / responder          |
| <b>Step 1b:</b>  |                            |               |                                    |
| - Step 1a + adjustment made to control arm to account for low dose mannitol  |                            |               |                                    |
| Costs  | \$ [redacted] <sup>a</sup> | \$0           | \$ [redacted]                      |
| 'Responders' Wk 14   | 0.5097                     | 0.4644        | 0.045                              |
| Incremental cost/extra patient responding  |                            |               | \$ [redacted] / responder          |
| <b>Step 2a:</b>  |                            |               |                                    |
| - Absolute change in ppFEV <sub>1</sub> from baseline at Wk 26 in Trials CF-301/CF-302                                     |                            |               |                                    |
| - Mannitol drug cost; assuming average treatment duration in Trials CF-301/CF-302 (21 weeks)                               |                            |               |                                    |
| Costs  | \$ [redacted]              | \$0           | \$ [redacted]                      |
| Absolute ΔppFEV <sub>1</sub> Wk 26   | 2.58                       | -0.13         | 2.71                               |
| Incremental cost/additional improvement in ppFEV <sub>1</sub>  |                            |               | \$ [redacted] / ppFEV <sub>1</sub> |
| <b>Step 2b:</b>  |                            |               |                                    |
| - Step 2a + adjustment made to control arm to account for low dose mannitol  |                            |               |                                    |
| Costs  | \$ [redacted]              | \$0           | \$ [redacted]                      |
| Absolute ΔppFEV <sub>1</sub> Wk 26   | 2.58                       | -0.8          | 3.38                               |
| Incremental cost/additional improvement in ppFEV <sub>1</sub>  |                            |               | \$ [redacted] / ppFEV <sub>1</sub> |
| <b>Step 3a:</b>  |                            |               |                                    |
| - Absolute change in ppFEV <sub>1</sub> from baseline at Wk 26 in Trials CF-301/CF-302, excluding 'non-responders' at wk14 |                            |               |                                    |
| - Mannitol drug cost; assuming average treatment duration in Trials CF-301/CF-302 (21 weeks)                               |                            |               |                                    |
| Costs  | \$ [redacted]              | \$0           | \$ [redacted]                      |
| Absolute ΔppFEV <sub>1</sub> Wk 26   | 5.76                       | 0.01          | 5.75                               |
| Incremental cost/additional improvement in ppFEV <sub>1</sub>  |                            |               | \$ [redacted] / ppFEV <sub>1</sub> |
| <b>Step 3b:</b>  |                            |               |                                    |
| - Step 3a + adjustment made to control arm to account for low dose mannitol  |                            |               |                                    |
| Costs  | \$ [redacted]              | \$0           | \$ [redacted]                      |
| Absolute ΔppFEV <sub>1</sub> Wk 26   | 5.74                       | -0.66         | 6.4                                |
| Incremental cost/additional improvement in ppFEV <sub>1</sub>  |                            |               | \$ [redacted] / ppFEV <sub>1</sub> |
| <b>Step 4:</b>   |                            |               |                                    |
| - LYs in the modelled evaluation over 100 year (lifetime) time horizon   |                            |               |                                    |
| - All modelled costs   |                            |               |                                    |
| Costs (discounted)   | \$ [redacted]              | \$ [redacted] | \$ [redacted]                      |
| LYs (discounted)   | 14.58                      | 13.90         | 0.68                               |
| Incremental cost/LY gained   |                            |               | \$ [redacted] / LYG                |
| <b>Step 5:</b>   |                            |               |                                    |
| - QALYs in the modelled evaluation over 100 year (lifetime) time horizon   |                            |               |                                    |
| - All modelled costs   |                            |               |                                    |
| Costs (discounted)   | \$ [redacted]              | \$ [redacted] | \$ [redacted]                      |
| QALYs (discounted)   | 13.12                      | 12.42         | 0.70                               |
| Incremental cost/QALY  |                            |               | \$ [redacted] <sup>^</sup> / QALY  |

<sup>a</sup> there was a slight discrepancy (likely due to rounding) versus the resubmission's result of \$ [redacted]

Source: Table D.5.8, p231 of the resubmission.

6.36 The redacted table shows an ICER in the range of \$15,000 - \$45,000/QALY.

- 6.37 The ESC noted that the resubmission adjusted the response rates in Trials CF-301 and CF-302 to attempt to remove the effect of the low dose of mannitol (of 50 mg twice daily) in the control group, by applying -1.5% to changes in ppFEV<sub>1</sub> for <18 year olds in the model, based on data from Trial CF-204. The ESC noted that a mannitol dose finding study, Trial CF-202<sup>2</sup>, found that a dose of 40 mg of mannitol twice daily did not improve ppFEV<sub>1</sub>. Accordingly, the ESC considered the adjustment for low dose mannitol may not have been appropriate and biased the results in favour of mannitol.
- 6.38 Table 12 provides the results of the sensitivity analyses conducted during the evaluation. While the resubmission presented an ICER for the DNase user subgroup of \$45,000 – \$75,000 per QALY gained, the estimate assumed responders on mannitol have an increased risk of exacerbations, as opposed to a reduced risk in the base case. Correction of this error returned an ICER of \$15,000 - \$45,000 per QALY gained. The ESC considered that the comparison of this ICER with the base case for the broader population (of \$15,000 - \$45,000 per QALY gained) contradicted the clinical data which generally showed a smaller benefit in this subgroup and illustrated the lack of external validity of the modelled economic evaluation.

Table 12: Sensitivity analyses conducted during the evaluation

| Sensitivity analyses  | Incremental costs | Incremental QALYs | ICER (\$/QALY) |
|---|-------------------|-------------------|----------------|
| Base case   | \$█               | 0.6985            | \$█            |
| Base case (50,000 trials)   | \$█               | 0.6109            | \$█            |
| DNase users only (100% DNase costed)  | \$█               | 0.6966            | \$█            |
| All patients cease mannitol after cycle 3 (Week 26)   | \$█               | 0.6146            | \$█            |
| All patients cease mannitol after cycle 7 (Week 74)   | \$█               | 0.6906            | \$█            |
| No ΔppFEV <sub>1</sub> due to age ≥30   | \$█               | 0.5842            | \$█            |
| No ΔppFEV <sub>1</sub> due to age ≥30 or exacerbations  | \$█               | 0.5575            | \$█            |
| No reduced risk of exacerbations on mannitol  | \$█               | 0.6674            | \$█            |
| Cost of treating exacerbations included <sup>a</sup> (\$█)  | \$█               | 0.6985            | \$█            |
| No benefit after ceasing mannitol   | \$█               | 0.4196            | \$█            |
| No benefit after ceasing mannitol + no reduced risk of exacerbations on mannitol  | \$█               | 0.4058            | \$█            |
| No benefit after ceasing mannitol + no reduced risk of exacerbations on mannitol + No ΔppFEV <sub>1</sub> due to age ≥30 or exacerbations   | \$█               | 0.2424            | \$█            |
| No benefit after ceasing mannitol + no reduced risk of exacerbations on mannitol + No ΔppFEV <sub>1</sub> due to age ≥30 or exacerbations + Cost of treating exacerbations included (\$█) | \$█               | 0.2424            | \$█            |

<sup>a</sup> The cost of treatment and hospitalisation for exacerbations was not explicitly incorporated into the base case of the economic model, as it was implicitly incorporated into the costs of managing CF.

Source: constructed during the evaluation

- 6.39 Overall, the univariate sensitivity analyses indicated that the model was largely insensitive to variables which do not radically alter the associated survival benefit attributed to mannitol in the model. Nevertheless, the Cox survival model which

<sup>2</sup> Teper, A., Jaques, A. and Charlton, B. Inhaled mannitol in patients with cystic fibrosis: A randomised open-label dose response trial. *Journal of Cystic Fibrosis* 2011; 10: 1-8.

underpinned the relationship between ppFEV<sub>1</sub> and mortality could not be adequately tested during the evaluation.

- 6.40 The PSCR (p4) argued the sensitivity analysis in which ppFEV<sub>1</sub> immediately returned to the baseline value when patients ceased mannitol (resulting in an ICER of \$45,000 – \$75,000 per QALY gained) was biased, as assumed that patients who previously received mannitol + BSC experience a faster rate of decline in ppFEV<sub>1</sub> than patients previously treated with BSC alone. However, the ESC considered this sensitivity analysis still favoured mannitol, as patients in real life are likely to have declining ppFEV<sub>1</sub> prior to cessation of mannitol, rather than experiencing an immediate drop, and will have reduced survival gain as a consequence. The ESC considered that the final sensitivity analysis presented in Table 12 (with an ICER of \$75,000– \$105,000 per QALY gained) still favoured mannitol as well as it estimated a median survival benefit of around 1.5 years and a median age of death of over 50 years in a population that included approximately 50% mannitol non-responders with some patients only having had one dose of mannitol. The pre-PBAC response (p2-3) argued that this the assumptions chosen for this multivariate analysis generated a worst-case ICER.

**Drug cost/patient/year: \$ [REDACTED]**

- 6.41 \$ [REDACTED] per month and \$ [REDACTED] per patient per year assuming the effective DPMQ of \$ [REDACTED] with 5% price reduction from 1 April 2018 and [REDACTED], and a maximum quantity pack lasting for 56 days.

**Estimated PBS usage & financial implications**

- 6.42 This resubmission was not considered by DUSC. The resubmission mainly used an epidemiological approach, based on data from the mannitol compassionate use program, to estimate the extent of mannitol combination use. At year 5, the estimated number of patients being treated with mannitol in combination with DNase was less than 10,000 and the net cost to the PBS would be less than \$10 million.

**Table 13: Estimated use and financial implications**

|   | Year 1 <sup>a</sup> | Year 2        | Year 3        | Year 4        | Year 5        |
|---|---------------------|---------------|---------------|---------------|---------------|
| <b>Estimated extent of use</b>                  |                     |               |               |               |               |
| Number treated (combination use on the PBS)     | [REDACTED]          | [REDACTED]    | [REDACTED]    | [REDACTED]    | [REDACTED]    |
| Packs <sup>b</sup> (combination use on the PBS) | [REDACTED]          | [REDACTED]    | [REDACTED]    | [REDACTED]    | [REDACTED]    |
| <b>Estimated net cost to PBS/MBS</b>            |                     |               |               |               |               |
| Net cost to PBS                                 | \$ [REDACTED]       | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Net cost to MBS                                 | \$ [REDACTED]       | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| <b>Estimated total net cost</b>                 |                     |               |               |               |               |
| Net cost PBS/MBS                                | \$ [REDACTED]       | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |

<sup>a</sup> Year 1 refers to the financial year 2017/2018 in the resubmission's analysis. The resubmission acknowledged that the revised PBS listing will come into effect mid-way through 2017/2018.

<sup>b</sup> 2.5 mannitol maximum quantity packs per patient per year.

Source: Compiled during the evaluation

- 6.43 The ESC agreed with the evaluation that it was not reasonable to assume the number of patients per year likely to be treated with mannitol in combination with DNase on the PBS will equate to the number of compassionate use patients in Australia. The PSCR (p5) agreed that the number of patients accessing combination use with DNase on the PBS is likely to be higher than current compassionate use as only 9 of the 24 Australian CF centres currently participate in the compassionate use program. The submission presented a sensitivity analysis for the utilisation and financial estimates assuming that █ patients from each of the 24 centres would seek treatment with PBS subsidised mannitol in combination with DNase which increased the number treated from █ to █ in Year 5. The ESC considered that the estimates of patients using combination therapy were uncertain and that the financial estimates were sensitive to this assumption.
- 6.44 The evaluation considered that the number of packs of mannitol dispensed on the PBS could also be higher than predicted. At the recommended dosage of 400mg twice daily, if patients were to take mannitol regularly for the full year, then █ packs rather than the estimated █ packs of mannitol would be required each year. The PSCR (p6) argued, with reference to the October 2014 DUSC review, PBS usage of mannitol has been lower than anticipated and it would be unreasonable to assume that patients treated with combination therapy would receive █ packs per year. The ESC noted the number of packs used per patient per year was uncertain and that the financial estimates were sensitive to this assumption.

### ***Quality Use of Medicines***

- 6.45 The resubmission stated that the quality use of mannitol would be ensured through the provision of resources to patients and CF clinics.

### ***Financial Management – Risk Sharing Arrangements***

- 6.46 The current Deed of Agreement between the Commonwealth of Australia and the Sponsor in relation to sharing the costs of the Commonwealth subsidy for the supply of mannitol (2012) includes a rebate and subsidisation caps. The submission proposed no changes to this Deed under the requested change to the current listing.
- 6.47 The current █, and the additional F1 5% statutory price reduction that will be effective in April 2018 (following 5 years of PBS listing in monotherapy), were factored into the mannitol price in the economic analysis and financial estimates. The ESC noted that including the F1 statutory 5% price cut that will apply to mannitol in April 2018 was contrary to the PBAC Guidelines that state that submissions should value future costs at current prices (PBAC Guidelines, Version 5.0 p.82).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended that the current Section 100 (Highly Specialised Drugs Program) listing of mannitol be amended to allow for PBS-subsidised use in combination with PBS-subsidised DNase in patients who are inadequately responsive to monotherapy with DNase.
- 7.2 The PBAC recommended that the NOTE in the current restriction for mannitol prohibiting use in combination with PBS-subsidised DNase be removed. Similarly, the PBAC recommended that a flow-on change be made to the restriction for DNase to remove the corresponding NOTE prohibiting use in combination with PBS-subsidised mannitol. However, the PBAC maintained that patients must be intolerant or inadequately responsive to DNase to be eligible for PBS-subsidised mannitol. The PBAC considered that patients should also have trialled hypertonic saline before combination therapy with mannitol and DNase and recommended that this requirement be added to the clinical criteria for mannitol (“Patient must have trialled hypertonic saline before combination use of mannitol and dornase alfa.”).
- 7.3 The PBAC acknowledged the consumer comments received, both from people living with the condition and on behalf of patients and their carers, in support for subsidised access to mannitol in combination with DNase. In particular, the PBAC noted equity concerns regarding access to combination treatment, given that mannitol is currently only available in combination with PBS-subsidised DNase through a compassionate use program, which can make prescribing complex for clinicians and patients.
- 7.4 The PBAC recalled that in March 2011 it rejected a submission for mannitol on the basis of uncertain effectiveness and resulting uncertain cost-effectiveness, when used in combination with DNase. Mannitol was subsequently recommended for monotherapy in patients inadequately responsive or intolerant to DNase in March 2012. The PBAC also recalled that in July 2015 it considered a minor submission for mannitol which requested removal of the NOTE prohibiting combination therapy with DNase on the basis of the difference between TGA approved indication (for both monotherapy and as an add-on to DNase) and the PBS restriction. The PBAC rejected the minor submission, as it did not address the issues raised by the PBAC in March 2011.
- 7.5 The PBAC noted, given the current compassionate access program use, that there is a clinical place for combination treatment with mannitol and DNase for a small number of patients with CF. The PBAC considered that clinicians will use their judgement in determining which patients would benefit from combination treatment. The PBAC noted the sponsor’s argument in its pre-PBAC response (p1) that patients with CF receive a range of treatments and tend to cycle on and off therapies depending on their current health status.

- 7.6 The PBAC considered that placebo/control + BSC (which may or may not include DNase) was not the appropriate comparator for the requested additional use of mannitol on the PBS, as an add-on therapy to DNase. Rather, the appropriate comparator was placebo + optimised DNase.
- 7.7 The PBAC noted that the resubmission was largely based on the ITT populations from Trials CF-301/CF-302 that included patients not receiving concomitant treatment with DNase. Accordingly, the PBAC noted that the evidence presented in the submission did not directly inform the requested additional population of patients who are inadequately responsive to optimised DNase and seek to add mannitol to existing DNase therapy. The PBAC considered that the resubmission inappropriately excluded Trial CF-203, a head-to-head crossover trial of mannitol + DNase versus the two agents administered as monotherapy. The PBAC noted that the combination of mannitol and DNase in this trial showed no change from baseline to endpoint in mean change in FEV<sub>1</sub> and appeared to perform worse than either treatment administered separately (although these differences were not statistically significant). However, the PBAC acknowledged that patients in Trial CF-203 were not on optimised DNase before the treatment period. The PBAC considered that it would be difficult to adequately power a trial to show statistically significant differences in this population and it is unlikely that any new clinical evidence will become available. Overall, the PBAC considered that there is likely to be a small group of patients inadequately responsive to DNase who would benefit from combination treatment and that clinicians would be best placed to identify those patients likely to derive a benefit.
- 7.8 The PBAC considered that the model did not provide a reliable indication of the cost-effectiveness of the comparison relevant to the requested change to the current listing; i.e. mannitol and DNase, compared with optimised DNase and placebo. However, the PBAC pragmatically considered that with a reduction in the requested price of mannitol for combination use, in recognition that combination treatment will not be as cost effective as monotherapy, the cost-effectiveness of the combination would be acceptable. This recommendation was made in the context of the small additional patient population with complex needs, equity of access concerns regarding the current compassionate use arrangements, an expectation that clinicians are best placed to determine which patients will benefit from combination therapy and no changes to the current risk sharing arrangements for mannitol. The PBAC advised the Department that a sizeable reduction in the price of mannitol for combination use would be appropriate to reduce the uncertainty regarding cost effectiveness.
- 7.9 The PBAC considered that the estimates of patients likely to use combination therapy were uncertain and that the financial estimates were sensitive to the assumptions regarding the number of packs dispensed per year. The PBAC noted that the submission base case estimates of utilisation only took into account current

compassionate access use, resulting in an estimate of ■■■ patients in year 5 of listing. The PBAC considered that the sensitivity analysis presented in the submission, which assumed ■ patients from each of the 24 CF centres would receive combination treatment (resulting in an estimated ■■■ patients in year 5 of listing), was more realistic. However, in the context of PBS use of mannitol monotherapy being lower than anticipated (as noted in the October 2014 DUSC review), the PBAC considered that the current risk sharing arrangements for mannitol were sufficient to manage the financial risk to the Government.

- 7.10 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 or where the PBAC makes a positive recommendation.

**Outcome:**

Recommended

**8 Recommended listing**

- 8.1 Amend existing listing as follows (with additions in italics and deletions in strikethrough):

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

|                                    |  |
|------------------------------------|--|
| <b>Category / Program</b>          | Section 100 – Highly Specialised Drugs Program   |
| <b>PBS Indication:</b>             | Cystic fibrosis  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing (Private hospital)<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input checked="" type="checkbox"/> Streamlined (Public hospital)                         |
| <b>Clinical criteria:</b>          | Patient must have been assessed for bronchial hyperresponsiveness as per the TGA approved Product Information initiation dose assessment for this drug, prior to therapy with this drug, with a negative result,<br>AND<br>Patient must be intolerant or inadequately responsive to dornase alfa.<br>AND<br><i>Patient must have trialled hypertonic saline before combination use of mannitol and dornase alfa.</i> |
| <b>Population criteria:</b>        | Patient must be 6 years of age or older.   |

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|                                |  |
|--------------------------------|--|
| <b>Prescriber Instructions</b> | <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 therapy with this drug, a baseline measurement of forced expiratory volume in 1 second (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 this drug 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 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. Therapy with this drug should cease if there is not general agreement of benefit as there is always the possibility of harm from unnecessary use.</p> |
| <b>Administrative Advice</b>   | <p><del>This drug is not PBS-subsidised for use in combination with PBS-subsidised dornase alfa.</del></p> <p>It is highly desirable that all patients be included in the national cystic fibrosis patient database.</p>   |

- 8.2 A flow-on change is required for the listings of dornase alfa (PBS item numbers: 5704F and 6120D) to remove the NOTE 'This drug is not PBS-subsidised for use in combination with PBS-subsidised mannitol'.

## 9 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.

## 10 Sponsor's Comment

The sponsor (Pharmaxis) would like to thank the PBAC for their positive recommendation. Pharmaxis would also like to thank the cystic fibrosis (CF) community (patients, families, patient organisations and healthcare professionals) who provided consumer comments during the process. Pharmaxis is committed to working with the PBAC and Pricing departments in order to ensure Australian CF patients receive timely access to Bronchitol.