

# Mannitol dry powder for inhalation for treating cystic fibrosis

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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# 1 Guidance

1.1 Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:

- who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase  
**and**
- whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV<sub>1</sub>] decline greater than 2% annually)  
**and**
- for whom other osmotic agents are not considered appropriate.

1.2 People currently receiving mannitol whose cystic fibrosis does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

## 2 The technology

- 2.1 Mannitol (Bronchitol, Pharmaxis) is a mucoactive agent that causes water to enter the airway lumen and hydrate airway secretions. This reduces the viscosity of secretions and stimulates cough, thereby increasing the clearance of secretions and pathogenic bacteria. Mannitol dry powder is inhaled from a hand-held, breath-activated device. Mannitol has a marketing authorisation as an add-on therapy to best standard of care in adults with cystic fibrosis. The summary of product characteristics states that the recommended dose is 400 mg twice a day.
- 2.2 The most common and important adverse reactions associated with mannitol as stated in the summary of product characteristics are hyperresponsiveness to mannitol, cough, bronchospasm, exacerbation of cystic fibrosis, chest discomfort, wheezing, throat irritation, vomiting, headache and pharyngolaryngeal pain. The most clinically significant adverse reaction associated with mannitol use is haemoptysis (coughing up of blood).
- 2.3 Mannitol is available as a 40 mg powder capsule for inhalation. The list price for a 14-day pack of 280 capsules and 2 inhalers is £231.66 (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] September 2012). This equates to £0.83 per 40 mg capsule, or an average cost of £16.55 per day, including the cost of the inhaler. These prices do not include VAT. Costs may vary in different settings because of negotiated procurement discounts.

### 3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of mannitol and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

#### Clinical effectiveness

- 3.1 The manufacturer presented clinical-effectiveness data from 2 randomised multinational double-blind controlled trials (DPM-CF-301 and DPM-CF-302). The trials were designed to assess the effectiveness of twice-daily mannitol at a dose of 400 mg compared with a 50 mg dose of mannitol twice daily, assumed to be sub-therapeutic. Patients in both arms also received best supportive care with or without rhDNase. Best supportive care included, but was not limited to, inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes, and antidiabetic agents for people with diabetes. The trials had 26-week double-blind phases, followed by further unblinded phases of 26–52 weeks. The inclusion and exclusion criteria for the 2 trials were similar but differed in the lower cut-off for 'FEV<sub>1</sub>% predicted' (FEV<sub>1</sub>% of the patient adjusted for the average FEV<sub>1</sub>% in the population for any person without cystic fibrosis of similar age, sex and body composition); this was 30% in DPM-CF-301 and 40% in DPM-CF-302.
- 3.2 DPM-CF-301 included 295 patients (190 adults) and took place at 40 centres in Australia, New Zealand, the UK and Ireland. The manufacturer presented results for adults only, in line with the marketing authorisation. There were 114 adults in the mannitol arm, of whom 58 used rhDNase and 56 did not use rhDNase, and 76 adults in the control arm, of whom 44 used rhDNase and 32 did not use rhDNase. There were 30 adults in the mannitol arm and 13 in the control arm (43 in total) who could not take rhDNase because of ineligibility, intolerance, or inadequate response to rhDNase. The remaining 45 patients did not use rhDNase for other reasons that were not recorded.
- 3.3 DPM-CF-302 included 305 patients (151 adults) and took place at 53

centres in the USA, Canada, Argentina, Germany, Belgium, France and the Netherlands. The manufacturer presented results for adults only. There were 93 adults in the mannitol arm, of whom 64 used rhDNase and 29 did not use rhDNase, and 58 adults in the control arm, of whom 41 used rhDNase and 17 did not use rhDNase. There were 15 adults in the mannitol arm and 7 in the control arm (22 in total) who could not take rhDNase because of ineligibility, intolerance, or inadequate response to rhDNase. The remaining 24 patients did not use rhDNase for other reasons that were not recorded. After a request by the ERG for clarification, the manufacturer submitted information on 2 groups defined by their use of rhDNase: (1) people using rhDNase and (2) people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.

- 3.4 The trial protocols for DPM-CF-301 and DPM-CF-302 were similar. Because mannitol and hypertonic saline have similar modes of actions, patients taking nebulised hypertonic saline were excluded from DPM-CF-301 and, in DPM-CF-302, patients could use nebulised hypertonic saline at initial assessment but had to stop 4 weeks before the baseline assessment. Potential participants were screened for bronchial hyperresponsiveness to mannitol, and those with hyperresponsiveness were excluded before randomisation. Randomisation was stratified by region and rhDNase use. The studies were powered to show an improvement in FEV<sub>1</sub> in both patients who took rhDNase and also the total trial population. There were 4 follow-up visits after the screening visit, at week 0 (start of treatment with mannitol or control) and at weeks 6, 14, and 26. In both trials, patients were offered the opportunity to continue or start mannitol treatment in an open-label phase for a further 26 weeks to gain more information on adverse reactions; in DPM-CF-301, there was an additional open-label extension phase of 26 weeks, giving a total of 78 weeks.
- 3.5 The primary outcome in both trials was the absolute FEV<sub>1</sub> as measured in millilitres over 26 weeks. Both trials reported changes in FEV<sub>1</sub> from baseline in the mannitol group compared with the control group.
- 3.6 Secondary outcomes included the proportion of patients who responded by FEV<sub>1</sub> criteria defined as achieving an increase from baseline of at least

100 ml in FEV<sub>1</sub>, or at least a 5% increase in absolute FEV<sub>1</sub> in millilitres, or at least a 5 percentage point increase in FEV<sub>1</sub>% predicted. Protocol-defined pulmonary exacerbations (PDPE) were defined as pulmonary events with 4 or more pre-defined symptoms or signs needing intravenous antibiotics. Reductions in the frequency of both PDPE and hospital care were measured in both trials.

- 3.7 Both trials measured quality of life using the Cystic Fibrosis Questionnaire – Revised (CFQ-R); DPM-CF-302 also used the Health Utility Index 2 (HUI2). The CFQ-R was administered to patients at week 0 and then at weeks 14 and 26. Antibiotic use and adverse events were also measured in both trials.
- 3.8 In the manufacturer's original submission, lung function was reported only for the subgroup of adults using rhDNase, in line with the fact that only 1 subgroup was pre-specified in the statistical plan of the study protocol. After a request by the ERG for clarification, the manufacturer submitted data on change in FEV<sub>1</sub> and exacerbations for adults using rhDNase and also for adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.
- 3.9 In the DPM-CF-301 trial, mannitol statistically significantly improved lung function over 26 weeks compared with the control, as measured by a change in FEV<sub>1</sub> from baseline of 109.3 ml (95% confidence interval [CI] 52.8 to 165.8; p<0.001) in adults using rhDNase. This difference was evident at 6 weeks of treatment and was maintained over the 26-week double-blind phase. For the other measures of lung function, the mean difference from baseline between adults randomised to receive mannitol plus rhDNase compared with the control group were: mean percentage change in FEV<sub>1</sub> from baseline of 4.2% (95% CI 0.3 to 8.1); change in FEV<sub>1</sub>% predicted of 2.7% (95% CI 0.6 to 4.7) and change in forced vital capacity (FVC) of 117.4 ml (95% CI 1.0 to 233.9). After a request for clarification, the manufacturer provided the change in FEV<sub>1</sub> over 26 weeks for the 43 adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase; this was 147.0 ml, a difference that was statistically significant between the mannitol and control group (95% CI 23.2 to 270.7, p=0.02).



- 3.10 In the DPM-CF-301 trial, for people using rhDNase, the incidence of PDPE (over the 26-week time horizon of the trial) was 27.6% for adults randomised to mannitol compared with 36.4% in the control group. For adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the incidence of PDPE was 16.7% in the mannitol group compared with 30.8% in the control group. The rate of PDPE per year was 1.41 for adults receiving mannitol plus rhDNase compared with 1.58 in the control group. The estimated PDPE rate per year was 0.41 for adults randomised to receive mannitol who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase compared with an estimated 0.64 in the control group. There was a 36.5% reduction in the rate of exacerbations in the mannitol group compared with the control group for patients who could not use rhDNase, but this was not statistically significant. The trials were not powered to demonstrate statistically significant differences for PDPE outcomes in these subgroups.
- 3.11 In the DPM-CF-302 trial, the mean change in FEV<sub>1</sub> over 26 weeks for adults using rhDNase and randomised to receive mannitol was not statistically significantly different from the control group (88.5 ml, 95% CI -8.5 to 185.4). For the other measures of lung function in adults using rhDNase randomised to receive mannitol compared with the control group, the mean difference in the changes from baseline were 5.4% (95% CI -0.4 to 11.3) for FEV<sub>1</sub>, 3.0% (95% CI -0.6 to 6.5) for change in FEV<sub>1</sub>% predicted and 96.9 ml (95% CI -7.7 to 201.6) for changes in FVC. After clarification, the manufacturer provided the difference in the change in FEV<sub>1</sub> over 26 weeks for mannitol in 22 adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase compared with the control group; this was 208.6 ml (95% CI -9.3 to 426.5, p=0.061).
- 3.12 In the DPM-CF-302 trial, the incidence of PDPE (over the 26 weeks of the trial) was 18.8% in adults using rhDNase alone compared with 9.8% for adults receiving mannitol plus rhDNase. For adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the PDPE incidence was 13.3% for adults randomised to mannitol compared with 42.9% in the control group. The estimated PDPE rate per year was 0.83 for adults randomised to mannitol plus rhDNase

compared with 0.19 in the control group. The estimated PDPE rate per year was 0.26 for adults randomised to receive mannitol who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase compared with an estimated 0.86 in the control group. However, the trials were not powered to demonstrate statistically significant differences for these outcomes in patients not receiving rhDNase or patients who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.

- 3.13 In response to the appraisal consultation document (ACD), the manufacturer presented analyses pooling the results of the DPM-CF-301 and DPM-CF-302 trials. The outcomes in the pooled analyses did not include the primary outcome, absolute FEV<sub>1</sub>, but instead were FEV<sub>1</sub>% predicted, the proportion responding according to FEV<sub>1</sub> criteria, and the estimated rate of PDPE per patient per year. For the pooled adult population of people using rhDNase, the mean change in FEV<sub>1</sub> over 26 weeks for patients receiving mannitol plus rhDNase was 94.1 ml (95% CI 29.7 to 158.42). For people who received mannitol but did not take rhDNase (irrespective of the reason), the change was 110.3 ml (95% CI not given, p<0.005). The change was 166.7 ml (95% CI 52.0 to 280.6) for the subgroup of adults receiving mannitol who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The pooled results for both trials for adults who could not use rhDNase were 0.27 PDPE per year in the mannitol group compared with 0.96 PDPE per year in the control group (not statistically significant).
- 3.14 The manufacturer reported on adverse events for the whole adult population, but not for the rhDNase subgroups based on rhDNase use. Overall, 87% of all adults experienced at least 1 adverse event, the most common adverse event being cough (the only adverse event that occurred in more than 10% of adults). However, the manufacturer considered productive cough a desired effect of treatment with mannitol. Other adverse events with an incidence of between 1% and 10% over 26 weeks were decreased appetite, headache, haemoptysis, bronchospasm, wheezing, asthma, condition aggravated, pharyngolaryngeal pain, and chest discomfort.
- 3.15 Haemoptysis was the most clinically significant adverse event in both

studies and was observed in 11.9% of adults on treatment with mannitol and 8.5% in the control group in the DPM-CF-301 trial, and in 7.1% in the mannitol group and 2.5% in the control group in the DPM-CF-302 trial. In response to the ACD, the manufacturer submitted pooled analyses on haemoptysis events based on the protocol-defined criteria for PDPE. For all adults using rhDNase, 16.4% experienced haemoptysis in the mannitol group and 20.0% in the control group. For adults not using rhDNase, these figures were 14.1% in the mannitol group and 14.3% in the control group.

- 3.16 Health-related quality of life was only presented for the whole adult population in the original manufacturer's submission. There were no statistically significant changes in the CFQ-R domains in either trial for adults randomised to receive mannitol relative to the control group. The results suggested some improvement in the respiratory, physical and vitality domains of CFQ-R, but these did not achieve statistical significance. In DPM-CF-302, there was no statistically significant difference in HUI2 measurements between adults randomised to receive mannitol and the control group.
- 3.17 In response to the ACD, the manufacturer submitted the proportion of adults whose condition was considered to respond to treatment based on FEV<sub>1</sub> criteria for both trials. In the DPM-CF-301 trial, for adults using rhDNase, the condition responded in 41.4% in the mannitol group and 27.3% in the control group; for adults not using rhDNase, these figures were 60.7% in the mannitol group and 40.6% in the control group. In the DPM-CF-302 trial, for adults using rhDNase, the condition responded in 45.3% in the mannitol group and 39.0% in the control group; for adults not using rhDNase, these figures were 44.8% in the mannitol group and 44.8% in the control group.

## Cost effectiveness

- 3.18 The manufacturer developed a Markov health-state transition model, implemented as a patient-level simulation model evolving over the lifetime of the patient, and modelling 2 treatment options: treatment with inhaled mannitol and treatment without inhaled mannitol. The manufacturer did not model inhaled hypertonic saline as a treatment that

a patient may use with, or instead of, mannitol. The model assumed treatment with mannitol for lifetime or until drop-out (according to the rate modelled on the trials). The analysis had a time horizon of 100 years, at which point all patients would have died. The cycle lengths were taken from the time between visits in the 2 trials, and were 6 weeks for the first cycle, 8 weeks for the second cycle and 12 weeks for each subsequent cycle. The transition parameters between the health states depended on characteristics derived from the clinical trial such as age, history of pulmonary exacerbations and use of mannitol.

- 3.19 The health states in the model include cystic fibrosis, cystic fibrosis with improved respiratory symptoms, lung transplantation, death from cystic fibrosis, and death from an unrelated cause. At baseline, all patients enter the cystic fibrosis health state. As patients progress, if their FEV<sub>1</sub>% predicted falls below 30%, they enter the lung transplantation state in which they have a probability of receiving a transplant in subsequent cycles. The model includes a discontinuation rule under which patients whose condition does not respond to mannitol treatment within 6 weeks stop mannitol and switch to best standard of care. Modelled to mirror the clinical trial, the definition of a response is either a relative increase of 5% or more in absolute FEV<sub>1</sub> or an absolute increase of 100 ml or more in FEV<sub>1</sub> at week 6 from baseline. In subsequent cycles, a patient may switch between the health states of cystic fibrosis and cystic fibrosis with improved respiratory symptoms and back again, and patients in either state may experience a pulmonary exacerbation. Patient characteristics such as body mass index (BMI), age and FEV<sub>1</sub>% predicted are updated.
- 3.20 The manufacturer used clinical-effectiveness data from the DPM-CF-301 and DPM-CF-302 trials to obtain baseline values and some, but not all, transition parameters used in the model, such as FEV<sub>1</sub>% predicted at week 26, the probability of being a 'responder' at 26 weeks and the relative risk of pulmonary exacerbations for 'responders' to treatment. Other transition parameters were derived from the literature and from the commissioned BioGrid study using regression analysis, such as FEV<sub>1</sub>% predicted over time, the rate of exacerbations and mortality after lung transplant. The baseline characteristics (age, sex, BMI and FEV<sub>1</sub>% predicted) were taken from the pooled adult population from the DPM-CF-301 and DPM-CF-302 trials. The manufacturer also used data from

the trials to estimate the probability of response to mannitol, FEV<sub>1</sub>% predicted after 26 weeks of treatment, the effect of treatment on pulmonary exacerbations, and the probability of improvement in respiratory symptoms. The manufacturer estimated changes in FEV<sub>1</sub>% predicted and the risk of an exacerbation after baseline from the BioGrid retrospective observational study of disease progression in cystic fibrosis, which used data from Australia (the BioGrid data) and was commissioned by the manufacturer. The decline over time in FEV<sub>1</sub>% predicted was modelled dependent on age, age above 30 years, and pulmonary exacerbations (using hospital admissions as a proxy). The manufacturer estimated the relationship between FEV<sub>1</sub>% predicted and mortality rate from the BioGrid data using survival analyses. In the model, mortality depended on FEV<sub>1</sub>, exacerbations, age, sex, concurrent infection with *Burkholderia cepacia* and lung transplantation. After a request for clarification from the ERG, data on these variables were provided to update the model for patients who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.

- 3.21 Utility values were drawn largely from HUI2 data collected during the DPM-CF-302 trial; the manufacturer also included values from the literature for lung transplantation and pulmonary exacerbations. The baseline utility was taken as the mean overall HUI2 global utility score at baseline (0.899). The manufacturer calculated the change in utility between baseline and visit 3 or in week 14, or between baseline and the last visit in the case of early withdrawal. The manufacturer calculated the HUI2 global utility scores for each health state by adding the average change to the baseline utility. The increase in utility value for patients with improved symptoms was 0.009 in the control group and 0.019 in the mannitol group. The decrease in utility for patients without improved symptoms was 0.046 for patients in the control group and 0.022 in the mannitol group. Utility values were not linked directly to lung function. The HUI2 questionnaire was administered in the trial at weeks 0, 12 and 26, but had a recall period of 1 week, and so did not necessarily capture the effect of PDPEs on health-related quality of life at the time they occurred. Therefore, the manufacturer took utility data for PDPEs and post-lung transplantation from the literature. Adverse events had a negative impact on CFQ-R data in both trials.

- 3.22 The manufacturer calculated the costs of treatment with or without mannitol accumulated up to 26 weeks, but made no distinction between patients whose lung function improved and those whose did not. The model included costs related to pulmonary exacerbation and for the time periods before and after lung transplantation. Costs were taken from national reference costs. The manufacturer included costs for concomitant medications (mostly antibiotics) for both groups, and used a mean cost of £3253 in the mannitol group and £2972 in the control group (with a cost of £0 for the subclinical trial dose). In the trials, most patients were admitted to hospital at least once, and approximately 40% had a community visit during the 26-week randomised phase of the trial. Costs of pulmonary exacerbation were taken from the trial data. For patients receiving mannitol, the mean total cost of medications, community visits and hospitalisations without a PDPE in the 26-week trial period was £4391, and taking into account PDPE the cost was £12,852. From the trial, for patients in the control group, the mean total costs without PDPE were £4664 and with at least 1 PDPE were £10,354. The manufacturer used peri-transplant costs from the UK literature and resource use from the trial and patient records. The manufacturer applied a discount rate of 3.5% to both costs and benefits.
- 3.23 The manufacturer's base-case results indicated an incremental cost-effectiveness ratio (ICER) for mannitol compared with treatment without mannitol (best supportive care) of £47,095 per quality-adjusted life year (QALY) gained in adults using rhDNase and £41,074 per QALY gained in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.
- 3.24 The manufacturer undertook extensive scenario analyses and deterministic sensitivity analyses for the treatment of adults using rhDNase and for adults not using rhDNase (irrespective of the reason for non-use). The parameters that changed the ICER by more than 10% were:
- FEV<sub>1</sub>% predicted at baseline
  - the regression parameter estimate for mannitol treatment used to predict the FEV<sub>1</sub>% predicted after 26 weeks of treatment (that is, the effect of treatment)



- the relative risk of an exacerbation with mannitol relative to not using mannitol for people whose condition was considered to respond to treatment
- the relative risk of a subsequent exacerbation if there had been an exacerbation in the previous year
- hazard rate of death for the FEV<sub>1</sub>% predicted
- the utility decrement associated with an exacerbation
- the utility associated with no improvement in respiratory symptoms among patients using or not using mannitol
- the cost of an exacerbation.

3.25 The manufacturer also performed sensitivity analyses showing the effect of several parameters, including treatment failure after 1, 5, 10 and 20 years. The base-case model assumed that patients using mannitol maintained the difference in lung function over their lifetime. Not maintaining the improvements in FEV<sub>1</sub>% predicted over the long term had a large effect on the ICER. If the improvements in FEV<sub>1</sub>% predicted were maintained for only 1 year the ICER was £149,587 per QALY gained; if improvements were maintained for 5, 10 and 20 years, the ICERs were £86,981, £63,539 and £49,907 per QALY gained respectively. Other factors that had an impact on the ICER were the rate ratio of pulmonary exacerbations between people receiving and those not receiving mannitol, whether the discontinuation rule was applied, the relative risk of a PDPE if the patient experienced an exacerbation in the previous year, costs and utilities. The manufacturer concluded that the main factors affecting the ICER were:

- the cost of mannitol
- the relative risk of pulmonary exacerbations in the mannitol group
- the impact of pulmonary exacerbations on quality of life
- the FEV<sub>1</sub>% predicted when starting mannitol
- the improvement in FEV<sub>1</sub>% predicted on mannitol treatment
- the hazard rate of death for FEV<sub>1</sub>% predicted

- utility for patients whose symptoms do not improve.
- 3.26 After a request from the ERG, the manufacturer provided scenario analyses taking into account reduced adherence to treatments, which reduced the costs in the mannitol group. Using a lower mean adherence gave an ICER of £37,387 per QALY gained for mannitol compared with the control in adults using rhDNase, and £33,934 per QALY gained for mannitol compared with the control in adults not using rhDNase.
- 3.27 There was uncertainty around the relative risk of PDPE, and the model was sensitive to fluctuation in this parameter. Using the relative risk of exacerbation of 0.7 associated with treatment with mannitol for the total adult population (provided by the manufacturer in response to a request for clarification from the ERG), the ICER for mannitol compared with not using mannitol was £54,329 per QALY gained in adults using rhDNase and £27,673 per QALY gained in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. Using a relative risk of exacerbations based on adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the ICER per QALY gained was £19,828.
- 3.28 In the manufacturer's probabilistic sensitivity analyses, as an add-on therapy to best standard of care, mannitol had a 16.4% probability of being cost effective at an ICER of £30,000 per QALY gained and a 7.4% probability at an ICER of £20,000 per QALY gained. For non-users of rhDNase, mannitol had a 25.8% probability of being cost effective at an ICER of £30,000 per QALY gained and a 10.9% probability at an ICER of £20,000 per QALY gained. In response to a request from the ERG to estimate the cost effectiveness separately for adults using rhDNase and adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the manufacturer re-ran the probabilistic sensitivity analysis. This resulted in mean ICERs of £53,796 per QALY gained for adults using rhDNase and £30,080 per QALY gained for adults ineligible for rhDNase.
- 3.29 The manufacturer conducted 2 further subgroup analyses, one by baseline FEV<sub>1</sub>% predicted and the other among patients whose condition responded to treatment with mannitol by 6 weeks. The analyses showed that, as baseline FEV<sub>1</sub>% predicted declines, the ICER decreases. For



FEV<sub>1</sub>% predicted 80% or more, the ICERs were £56,228 per QALY gained for adults using rhDNase and £50,688 per QALY gained for adults not using rhDNase. For FEV<sub>1</sub>% predicted less than 40%, the corresponding ICERs were £30,746 per QALY gained for adults using rhDNase and £23,704 per QALY gained for adults not using rhDNase.

- 3.30 In response to the ACD, the manufacturer submitted a revised model for people with cystic fibrosis not using rhDNase, including people whose reason for not using rhDNase was not reported in the trials and is not known. In addition, the manufacturer changed several key parameters in the model. The health states in the model more closely model health states rather than treatment states. The costs and utility values in the revised model no longer depend on treatment, but rather on whether the simulated patient has improved respiratory symptoms or not. The utility values are no longer directly tied to lung function. The manufacturer also included a new stopping rule, centred on the Committee's concerns that a stopping rule based on an FEV<sub>1</sub> improvement as defined would be unlikely to be implemented in practice. In the new stopping rule, people are permitted to continue using mannitol if their FEV<sub>1</sub> improves by more than 0%, that is, if their FEV<sub>1</sub> improves at all. The manufacturer continued to base its model on the BioGrid data, but submitted evidence in an effort to show that the BioGrid population was similar to the UK population with cystic fibrosis. For people not using rhDNase, the manufacturer used a revised utility value of 0.896. In the original model, the change in utility value was 0.015 for people using mannitol who had improved respiratory symptoms, and 0.031 for people using mannitol who did not have improved respiratory symptoms. In the revised model, the change in utility value for people not using rhDNase and who took mannitol and had improved respiratory symptoms increased to 0.025 and for people who did not use rhDNase who took mannitol and had no improvement it decreased to 0.001. In the ERG's analyses, treatment for people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase had costs of £3885 if they improved and £4385 if they did not improve, a difference of £500. In the model developed in response to the ACD, treatment for people who did not use rhDNase had costs of £2307 if they improved and £3255 if they did not improve, a difference of £948. The manufacturer chose a baseline PDPE rate of 1.01, based on the ERG's critique of the original model.

- 3.31 The manufacturer did not provide revised estimates of cost effectiveness for the whole population. The revised ICER for mannitol compared with best supportive care was £19,993 per QALY gained in people not using rhDNase, and had an 82.2% probability of being cost effective at an ICER of £30,000 per QALY gained and a 46.5% probability at an ICER of £20,000 per QALY gained. Furthermore, the manufacturer provided a new analysis based on adherence rates of 30% and 70%. Keeping the QALYs constant, the ICER per QALY gained was £6327 at a compliance of 30% and £14,137 at a compliance of 70%.
- 3.32 The manufacturer submitted additional clinical evidence indicating that the relative benefit with respect to FEV<sub>1</sub> associated with taking mannitol was maintained over 78 weeks. This evidence derived from an extension of the 2 trials. The manufacturer also provided scenario analyses showing the ICERs for shortening the model's time horizon from lifetime (100 years) to 5, 10 and 50 years to be £45,329, £25,151 and £20,018 per QALY gained respectively.
- 3.33 In response to the ACD, the manufacturer also conducted a survey defining the treatment pathway for managing sputum in cystic fibrosis. The manufacturer noted that this survey showed 82% of people with cystic fibrosis have trialled hypertonic saline before age 18 years. The manufacturer stated that clinicians would be reluctant to change treatments for people with well-controlled cystic fibrosis. They also noted that approximately a third of people currently using hypertonic saline did not have well-controlled cystic fibrosis and may be able to benefit from mannitol.

## Evidence Review Group comments

- 3.34 The ERG regarded DPM-CF-301 and DPM-CF-302 as well designed, high-quality trials, with a large combined study population. The ERG noted the change in therapeutic indication of mannitol limiting it to adults, which reduced the combined study population to 341 and consequently reduced the statistical power of all the analyses.
- 3.35 The ERG conducted pooled analyses on the results of the DPM-CF-301 and DPM-CF-302 trials. These showed statistically significant

differences between mannitol and the control with all outcomes related to lung function. Among adults using rhDNase, the differences between mannitol and control over 26 weeks were as follows: 91.8 ml (95% CI 30.9 to 152.7) for change in FEV<sub>1</sub>, 4.6 (95% CI 1.3 to 7.8) for percentage change in FEV<sub>1</sub>, 2.7 (95% CI 0.9 to 4.5) for FEV<sub>1</sub>% predicted and 106.1 ml (95% CI 28.3 to 183.9) for FVC. The ERG analysed data from adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, rather than from the broader group of adults not using rhDNase because that reflected the anticipated marketing authorisation at that time, but the marketing authorisation was eventually not restricted to this group. For adults who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the change in FEV<sub>1</sub> from baseline was 162.3 ml (95% CI 51.8 to 272.9).

- 3.36 The ERG's pooled analyses showed that, for the adults using rhDNase, there were no statistically significant differences between the mannitol and control arm in incident PDPE over the 26 week trial period (relative risk [RR] 1.00, 95% CI 0.61 to 1.66), and no statistically significant difference in the estimated rate of PDPE per year (RR 1.14, 95% CI 0.75 to 1.73). In the group of people who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, there were also no statistically significant differences between mannitol and the control in the incidence of PDPE (RR 0.44, 95% CI 0.18 to 1.10) over the course of the trial. The ERG stated that restriction of the therapeutic indication to adults meant that the analysis was under-powered, a problem compounded by the post-hoc subgroup analyses of the pooled trial data, and contributed to the uncertainty around the results.
- 3.37 The ERG conducted an indirect comparison of mannitol with hypertonic saline, in line with the scope. The 2 measures common to the identified study of hypertonic saline (0.9% saline) (Elkins et al. 2006) and the DPM-CF-301 and DPM-CF-302 trials were measurements of FEV<sub>1</sub> and pulmonary exacerbations. The ERG found that mannitol improved FEV<sub>1</sub> compared with hypertonic saline, although this was statistically significant only for the subgroup that could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. FEV<sub>1</sub> was 94.3 ml (95% CI 29.0 to 159.6) higher with mannitol than with hypertonic saline, regardless of rhDNase use, and for adults using rhDNase FEV<sub>1</sub>

was 23.8 ml (95% CI –65.0 to 112.5) higher with mannitol than with hypertonic saline.

- 3.38 In the ERG's view, the basic structure of the manufacturer's Markov model was appropriate for the research question, sufficiently inclusive and diverse to model the complexities of cystic fibrosis, but the ERG expressed concerns about the cost-effectiveness model.
- 3.39 The ERG questioned the assumption by the manufacturer in the model that mannitol use was completely independent of rhDNase use (that is, that any benefit of mannitol did not depend on whether a patient used, or did not use, rhDNase). This led the ERG to re-analyse the data according to rhDNase use and to divide the group not using rhDNase into those who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and those who could use rhDNase but did not do so for unknown reasons.
- 3.40 The ERG indicated that there was statistically significant heterogeneity in the overall group of people not using rhDNase. Patients who were able to take rhDNase but did not do so had different characteristics than those who were unable to take rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The ERG noted that mannitol is more likely to provide effective treatment to people who cannot rather than do not take rhDNase and who do not take hypertonic saline.
- 3.41 The ERG noted that the manufacturer had not used the results of the trials in the model, but instead had developed regression equations to estimate lung function. The ERG felt that the use of regression was appropriate for this Markov patient-level model, and noted that the manufacturer had consulted with experts on cystic fibrosis and modelling. The manufacturer also ran a microsimulation (100,000 trials) to compare the model output with the pooled results of the DPM-CF-301 and DPM-CF-302 trials. The ERG found small mistakes in the manufacturer's model, but noted that the validation checks matched the results of the clinical studies at a time point of 26 weeks.
- 3.42 The ERG noted that one of the most important assumptions made by the manufacturer was that any absolute improvement in FEV<sub>1</sub>% predicted

relative to patients not using mannitol would be maintained throughout the lifetime of the patient, and would directly translate into lower rates of morbidity and mortality. That is, a patient on mannitol would experience a decline in lung function over time consistent with the natural history of disease but, on cessation of mannitol treatment, would start the decline at a higher level of FEV<sub>1</sub>% predicted than a patient not taking mannitol. The ERG was concerned that there were no long-term data to support this assumption. The ERG questioned the manufacturer's use of Australian BioGrid data for transition parameters, which may not be generalisable to the UK.

- 3.43 The ERG was concerned about several assumptions made by the manufacturer in the original model about pulmonary exacerbations, namely the narrow confidence intervals around the baseline rate based on the BioGrid data used in the deterministic sensitivity analysis, and questioned whether it applied to a UK population.
- 3.44 The ERG was concerned about assumptions made by the manufacturer in the original model that HUI2 utility and cost parameters depended on treatment, but not on health state. The ERG questioned that there was no direct link between lung function and utility and suggested that a model linking lung function to utility could have altered the cost effectiveness and could have decreased the ICER.
- 3.45 The ERG conducted exploratory analyses to examine the effect on the ICER of varying the model assumptions and the input parameters, including the difference in costs and utilities associated with respiratory symptoms and exacerbations, and the mortality rate of cystic fibrosis by varying the FEV<sub>1</sub>% predicted. However, because of a lack of data, the ERG could not investigate the manufacturer's assumption that the probability of moving between health states remained the same over the lifetime of the patient.
- 3.46 The ERG amended the model to include treatment-independent and improvement-specific values for costs and utilities; using rhDNase subgroup-specific relative risks associating treatment with exacerbations, changing the cost of rhDNase from £16.88 to the most recent price of £16.55 (British national formulary 61); and adjusting model

parameters, probabilities and distributions.

- 3.47 The ERG's exploratory cost-effectiveness analysis included the treatment options of best standard of care, rhDNase and mannitol, but not hypertonic saline. The ERG compared best standard of care with mannitol plus best standard of care. In people using rhDNase, best standard of care included rhDNase, and in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, best standard of care did not include rhDNase. These amendments resulted in the ERG's ICER for mannitol plus best supportive care compared with best supportive care of £80,098 per QALY gained in adults using rhDNase and £29,883 per QALY gained in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The main reasons for the changes to the ICERs were the use of health-state specific costs and utilities used by the ERG rather than treatment specific costs and utilities used by the manufacturer, and the population specific relative risks for exacerbations.
- 3.48 The ERG investigated the relationship between improvements in FEV<sub>1</sub>% predicted and survival, and found evidence to support the assumption that a 1 percentage point improvement in FEV<sub>1</sub>% predicted was related to an approximate 5% reduction in mortality.
- 3.49 The ERG examined the assumption that the improvement in FEV<sub>1</sub>% predicted caused by mannitol would be maintained over the lifetime of the patient by reducing the time horizon of the model as a proxy for a shorter duration of effectiveness. This was similar to a scenario analysis conducted by the manufacturer. The ERG's analyses in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase resulted in ICERs for a time horizon of 5 years of £90,126 per QALY gained. For a time horizon of 10 years, the ICER was £49,854 per QALY gained for people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase.
- 3.50 The ERG pointed out that the manufacturer had generated cost data based on whether a patient received mannitol or not, rather than whether the patient was in a given health state. The manufacturer divided costs according to respiratory symptoms or according to



rhDNase use, but did not estimate costs by both factors simultaneously. However, the ERG acknowledged that, in its revised model in response to the ACD, the manufacturer derived costs using patient-level data. The ERG used the information available to calculate the ratio of the improvement-specific costs to the overall mean costs as an estimate of the difference in costs by health state. The ERG calculated that patients with improved respiratory symptoms have 93% of the overall costs, whereas patients without improved symptoms have 105% of the overall costs. The ERG assumed these percentages also applied to mean costs with rhDNase. The ERG estimated 6-month treatment costs for improved and not improved respiratory symptoms in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The ERG decided that health-state specific costs should be used rather than treatment specific costs. The ERG confirmed that the manufacturer used treatment specific values in its revised analysis of people not using rhDNase.

- 3.51 The ERG re-ran the probabilistic sensitivity analyses with assumptions based on its exploratory analyses, varying the exacerbation rate in the control group, making the costs and utilities improvement specific rather than treatment specific, and using shorter time horizons. The ERG calculated that there was a zero probability that the ICER for mannitol would lie below £30,000 per QALY gained for people using rhDNase. For those who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, the probability that the ICER would be below £20,000 per QALY gained was 5%, and the probability it would be below £30,000 per QALY gained was 50%.
- 3.52 The ERG considered the health-related quality-of-life data provided by the manufacturer in the form of HUI2 data collected in the DPM-CF-302 trial, and questioned the use of treatment-dependent values for utility. For its own sensitivity analyses, the ERG used values for utilities received from the manufacturer in response to a request for clarification and assumed that these values were independent of treatment. The ERG did not identify any other substantial health-related benefits not included in the QALY.
- 3.53 The factors identified by the ERG as causing substantial differences in

the ICERs generated by the ERG and the manufacturer included whether or not someone took rhDNase alongside mannitol, the assumption that any improvement in FEV<sub>1</sub>% predicted caused by mannitol would be sustained over the patient's lifetime, the assumption that patients whose condition did not respond to mannitol would discontinue therapy, and the effect of pulmonary exacerbations on utility. The manufacturer addressed these in their response to the ACD and in the second Committee meeting by changing these assumptions to be in line with those used by the ERG.

- 3.54 In their response to the ACD, the manufacturer provided evidence to suggest that the BioGrid data were similar to the UK population with cystic fibrosis. The ERG explained to the Committee that there was a clinically meaningful difference in the FEV<sub>1</sub>% predicted values for the BioGrid data and the UK data (of 60.2% for the BioGrid data and 66.3% for the UK data) because every percentage point decrease in predicted FEV<sub>1</sub>% predicted has an impact on mortality.
- 3.55 The ERG highlighted the additional analyses in the manufacturer's response to the ACD, which supported its assumption that improvements in FEV<sub>1</sub>% predicted would be maintained throughout the lifetime of the patient. In the second Committee meeting, the ERG stated that there was uncertainty about whether the benefit of mannitol would persist over time, decrease at the same rate as that of the control group, or decrease at a slower rate. The ERG commented that a time horizon of 50 years was likely to accurately represent the lifetime horizon of the adult UK population with cystic fibrosis.
- 3.56 In examining the manufacturer's revised analysis in people who do not use rhDNase, the ERG identified 3 drivers that decreased the ICER from that in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase (as originally modelled): including the exacerbation rate chosen for the model; acknowledging that some people treated with mannitol stop taking it ('drop-outs'); and the change in the estimated price for best supportive care, with the difference between best supportive care and mannitol being smaller in the original model (£500) than in the revised model (£948).



3.57 Full details of all the evidence are in the manufacturer's submission and the ERG report.

## 4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of mannitol, having considered evidence on the nature of cystic fibrosis and the value placed on the benefits of mannitol by people with cystic fibrosis, the people who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

### Clinical practice

- 4.2 The Committee discussed the clinical needs of people with cystic fibrosis. It heard from clinical specialists that cystic fibrosis leads to considerable morbidity and early mortality, and that there is no single standard care pathway in the UK. Clinicians and patients working with cystic fibrosis centres decide on treatment according to each patient's needs. The clinical specialists added that the aim of treatment in adults is to maintain lung function (as measured primarily by the absolute volume of FEV<sub>1</sub> in millilitres), particularly after the age of 30 years. In response to the consultation, the clinical specialists added that it is particularly important to manage cystic fibrosis to prevent a further decline in lung function in patients with rapidly declining lung function (that is, more than 2% per year decline in FEV<sub>1</sub>% predicted). Clinicians and patients manage lung function primarily through efforts to reduce airway infections, increase airway clearance, aid sputum clearance and maintain body weight through good nutrition. The Committee heard from the clinical specialists that approximately 98% of people with cystic fibrosis are registered with cystic fibrosis centres, and that clinicians use the Cystic Fibrosis Trust guidelines as the basis for best standard of care. The Committee heard from the clinical specialists that, as with hypertonic saline, rhDNase is inhaled as a nebulised solution and is an adjunct to physiotherapy, along with inhaled, oral or intravenous antibiotics for *Pseudomonas aeruginosa*, and that use of rhDNase varies widely across the UK. The Committee concluded that best standard of care for cystic fibrosis was complex and tailored to patient needs, and that rhDNase treatment was considered a component of best standard of care.

4.3 The Committee considered the place of mannitol within the cystic fibrosis treatment pathway, particularly in relation to the use of hypertonic saline. It noted the therapeutic indication of mannitol as an add-on therapy to best standard of care. The Committee heard from the clinical specialists that, after treatment with rhDNase, a patient would be offered either mannitol or hypertonic saline. The clinical specialists stated that approximately 40% of patients in the UK are treated with hypertonic saline. However, the patient expert highlighted that the unpleasant taste and experience of hypertonic saline can lead to poor adherence and this was confirmed by the clinical specialists. The Committee considered whether mannitol could replace nebulised hypertonic saline, but noted that the decision problem and the marketing authorisation clearly defined mannitol as an add-on therapy, and it would not be expected to replace any component of current treatment. The Committee was aware that both of the trials presented by the manufacturer excluded patients taking hypertonic saline, and therefore that the manufacturer had not provided the Committee with any evidence of effectiveness of mannitol added on to hypertonic saline. At the second meeting, the manufacturer noted that, because mannitol and hypertonic saline have a similar mechanism of action (both are osmotic agents), the manufacturer did not expect that mannitol would be added on to a treatment regime containing hypertonic saline. Also, taking into consideration the treatment pathway survey provided by the manufacturer in response to the ACD, the Committee acknowledged that mannitol was unlikely to be used in most patients, and that mannitol would be used as an add-on therapy to best standard of care, but not as a replacement for hypertonic saline use in people with stable cystic fibrosis. The Committee also noted that the manufacturer in its response to the ACD proposed that mannitol should only be considered in people with cystic fibrosis for whom hypertonic saline is not appropriate.

4.4 The Committee considered a patient's experience of cystic fibrosis, which involves several treatments, and how patients would use mannitol. The patient expert explained the difficulties in adhering to treatments, and stated that using mannitol with an inhaler would be much easier than using hypertonic saline with a nebuliser and would likely encourage adherence. Again, the Committee was aware that the marketing authorisation for mannitol stipulates that it would add on to, rather than

replace, existing therapies. The Committee heard from the patient expert and clinical specialists that the treatment time for mannitol could be cut to 2–3 minutes twice a day with training and practice, whereas nebulised treatments take much longer. The patient expert also described the issues faced by carers, with increased burdens from both assisting with treatment and helping patients to maintain normal lives. The patient expert and clinical specialists stated that current therapies (particularly therapies delivered by nebulisers) are complex to set up and to deliver, and equipment needs careful cleaning, which adds to the treatment burden, as do the difficulties in travelling with nebuliser equipment. The patient expert also highlighted the cost to patients of treatments, which are not fully funded by the NHS. The Committee agreed that there were potential advantages to patients of having a wider choice of treatment options. The Committee concluded that cystic fibrosis and its management had a major impact on the quality of life of patients and their carers, and that mannitol could ease some of this burden because it is a dry powder for inhalation, is associated with fewer unpleasant effects, needs less costly equipment and needs less time to administer than nebulised treatments.

## Clinical effectiveness

- 4.5 The Committee noted that the manufacturer's original submission was in line with the anticipated marketing authorisation (treatment of cystic fibrosis in adults aged 18 years and over as an add-on therapy to rhDNase, and in patients ineligible for, intolerant of, or whose condition inadequately responded to, rhDNase), and did not reflect the current approved marketing authorisation (treatment of cystic fibrosis in adults as an add-on therapy to best standard of care). The Committee also noted that the population specified in the scope included children, and included rhDNase and hypertonic saline as comparators. The Committee noted that the group of all people not using rhDNase was a clinically heterogeneous group, and included patients who cannot use rhDNase, and patients who can but do not use rhDNase for reasons not recorded. The Committee heard from the clinical specialists that the use of rhDNase varies geographically within the NHS. The Committee concluded that the analyses carried out for the populations described as people using rhDNase and all people not using rhDNase would reflect the

population in the final marketing authorisation.

- 4.6 The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of mannitol. The Committee was concerned that the statistical power of the presented analyses was reduced by having to limit the population to adults, which reduced the population to almost half of the original trial population, as well as by differentiating according to rhDNase use, and then further according to the reasons for not using rhDNase. The Committee was also concerned that a considerable number of initial study participants did not proceed to randomisation. The Committee further noted that the analysis of the subgroups using and not using rhDNase was part of the trial protocol, but that the trials were powered for statistical significance only for the group using rhDNase, and not for the group not using rhDNase. The Committee concluded there were some concerns about the design of the trials and the resulting analyses, particularly with the post-hoc analyses and low statistical power, and that these factors increased the uncertainty in the results, including the possibility that real differences existed that the study did not demonstrate statistically.
- 4.7 The Committee heard from the manufacturer that 50 mg mannitol twice daily was used as the placebo in the trials after a request from regulatory authorities. The Committee heard from the manufacturer that it chose this dose from a dose-ranging study. Both the manufacturer and clinical specialists acknowledged that there was likely to be a small therapeutic effect at this dose, as also suggested by the FEV<sub>1</sub> increasing from baseline by 52.4 ml in the DPM-CF-302 trial in the control group. The Committee concluded that mannitol would be more effective than reported in the trials, if the placebo had had a clinical effect.
- 4.8 The Committee considered the outcomes used in the trials, and how these differed from the outcomes used in clinical practice in adults with cystic fibrosis. The Committee discussed the manufacturer's selection of absolute change in FEV<sub>1</sub> in millilitres in the trial and FEV<sub>1</sub>% predicted in the economic model, and the manufacturer's definition of 'responders' as people whose absolute FEV<sub>1</sub> improved by 100 ml or 5% or more, or whose FEV<sub>1</sub>% predicted improved by 5% points. The Committee heard from clinical specialists that both absolute FEV<sub>1</sub> and FEV<sub>1</sub>% predicted

measurements are used in clinical practice, that a change in absolute FEV<sub>1</sub> between 75 and 100 ml is clinically meaningful, and that FEV<sub>1</sub>% predicted is used for children and to compare across different adult patient populations. The clinical specialists explained that the manufacturer's definition of a response did not accurately reflect clinical practice in the UK. If a patient felt better, but did not reach the threshold defining response (for example, their absolute FEV<sub>1</sub> increased by only 80 ml), the clinician would be unlikely to recommend stopping treatment. The patient expert concurred, stating that lung function can vary from day to day, and that small changes could make a difference to daily life and activity. The Committee concluded that the FEV<sub>1</sub> response outcomes were clinically relevant, but that the definition of 'responders' in the original manufacturer's submission differed from UK practice.

- 4.9 The Committee considered whether the 2 trials presented were equivalent, as the eligibility criteria at the lower end of FEV<sub>1</sub>% differed between the 2 studies. The clinical specialists explained this was because DPM-CF-301 was conducted largely in the UK, and DPM-CF-302 largely in the US, where prophylactic antibiotics and rhDNase are used more frequently than in the UK, and because there are differences in the regulations of the Food and Drug Administration and European Medicines Agency pertaining to the lower limit of FEV<sub>1</sub>% predicted for inhaled substances. The Committee was concerned about the way in which the 2 trials were blinded, and whether functional unblinding existed. It was also concerned that mannitol may cause rebound bronchoconstriction, but acknowledged that patients had undergone a mannitol tolerance test before entering the trials, and also heard from the clinical specialists that rebound bronchoconstriction did not occur in the trials. Overall, the Committee concluded that the 2 trials presented were equivalent and that it was reasonable to pool the results, but that there were methodological concerns about the analysis of clinical outcomes in the studies, and that there may have been functional unblinding, which would increase uncertainty about the clinical effectiveness of mannitol.
- 4.10 The Committee discussed the issue that hypertonic saline was not included as a comparator in the manufacturer's submission, although it was included in the scope and the ERG's indirect comparison (see section 3.37). Being aware that the use of nebulised hypertonic saline

was an exclusion criterion in both the DPM-CF-301 and DPM-CF-302 trials, the Committee noted that there was no clinical-effectiveness data for mannitol in people who used hypertonic saline. The Committee heard from the manufacturer and the ERG that there were difficulties in comparing the 2 osmotic agents, in particular because of the heterogeneity in the outcome measures in the clinical trials of the 2 osmotic agents and the lack of definition of the concentration of hypertonic saline solution used in clinical practice in the UK. The Committee noted the Cochrane review of hypertonic saline for cystic fibrosis, and the apparent improvement in pulmonary exacerbations and quality of life compared with isotonic saline, and heard that the clinical specialists considered the review to have been well-performed and valid. The Committee noted that, despite the final marketing authorisation permitting the addition of mannitol to best standard of care, mannitol would be unlikely to be used as an add-on to hypertonic saline because mannitol and hypertonic saline have similar mechanisms of action (see section 4.3). However, because the lack of clinical evidence precluded the use of hypertonic saline as a comparator in the analysis, and because the Committee was not presented with any evidence demonstrating the effectiveness of mannitol in people using hypertonic saline, the Committee concluded that the only possible recommendation is for people for whom other osmotic agents are not considered appropriate. The Committee concluded that adults with cystic fibrosis who cannot take hypertonic saline, for example for reasons of intolerability, represent a population with unmet need who would be able to benefit from the use of mannitol. The Committee further concluded that a clinical trial would be needed to establish the relative effectiveness of mannitol compared with hypertonic saline.

- 4.11 The Committee considered the incidence of adverse reactions during the trials, and their effects on people with cystic fibrosis. The Committee heard from the clinical specialists that productive cough is seen as a positive effect whereas irritating cough is seen as negative, but noted that learning to control cough is an important part of managing cystic fibrosis. The patient expert discussed the experience of using current therapies, and how the negative effects (such as unpleasant taste and sensations) affect a person's daily life and increase the burden of treatment. The Committee considered the manufacturer's response to



the ACD and noted that mannitol was not more likely to cause haemoptysis than best supportive care. In the Committee's view, adverse reactions were not sufficiently captured by effects on quality of life through the HUI2 measurement in DPM-CF-302, given that a week could elapse between the adverse reaction and reporting, and the bias towards a higher chance of filling in the questionnaire when feeling well, rather than feeling ill. The Committee concluded that the treatment of cystic fibrosis can cause several moderate and severe adverse reactions, and that it can be difficult to establish the effect of adverse reactions on health-related quality of life in a disease as complex as cystic fibrosis.

- 4.12 The Committee noted that each trial collected quality-of-life data but that the manufacturer had not submitted EQ-5D data as preferred by NICE. The Committee heard from the clinical specialists and the patient expert that assessing quality of life in people with cystic fibrosis is very difficult because they often describe their quality of life as being equivalent to people without cystic fibrosis or without other chronic conditions. The patient expert explained that she perceived her life as 'normal', and had never known any other health state. The Committee recognised the difficulty in valuing health states in chronic conditions, but that the standard method of using the general population's valuation of descriptions of health-related quality of life to generate utility values was appropriate. The Committee concluded that current measures of quality of life may not accurately capture the consequences of having cystic fibrosis and of its treatments.
- 4.13 The Committee considered the relationship between absolute change in FEV<sub>1</sub> and pulmonary exacerbations. The Committee heard from the clinical specialists that FEV<sub>1</sub> and pulmonary exacerbations have not previously been shown to be directly related. The Committee noted that the average rate of pulmonary exacerbations was lower in people considered 'responders' than in 'non-responders' in DPM-CF-301. The Committee questioned that incidence of pulmonary exacerbations in people not using rhDNase was lower than in people using rhDNase in DPM-CF-301, but it was the other way around in DPM-CF-302, and the manufacturer could not explain this difference. The Committee was aware that the 36.5% relative risk reduction in the rate of exacerbations with mannitol compared with control in people not using rhDNase was



not statistically significant, but acknowledged that this could be a result of the post-hoc subgrouping (see section 3.10). On balance, however, the Committee acknowledged that it was plausible that absolute change in FEV<sub>1</sub> and pulmonary exacerbations could be related. The Committee concluded that mannitol is clinically effective in improving both lung function (FEV<sub>1</sub>) and pulmonary exacerbations in people with cystic fibrosis. The Committee further concluded that there are subgroups of people who may experience greater benefit from mannitol, such as people who cannot use rhDNase, but that there is a degree of uncertainty about the magnitude of any increased clinical effectiveness.

## Cost effectiveness

4.14 The Committee considered the manufacturer's cost-effectiveness analysis, and the ERG's critique and exploratory analyses. It noted that the manufacturer originally used a patient-level simulation model to evaluate the cost-effectiveness of mannitol compared with best standard of care in people using rhDNase and people ineligible for or intolerant of, or whose condition inadequately responded to, rhDNase. The Committee also noted that clinical-effectiveness data presented in the submission were not used directly in the model, instead the manufacturer derived transition parameters from the 2 mannitol trials and from the literature, and incorporated them into the model through regression analysis. In a response to the ACD, the manufacturer provided a revised cost-effectiveness model, addressing some of the Committee's concerns. The Committee noted that the structure of the original model was not a health-state model, but rather was a model of the cystic fibrosis treatment pathway. The Committee was aware of the ERG's concerns about the manufacturer's original assumptions that any improvement in FEV<sub>1</sub>% predicted would be maintained throughout the lifetime of the patient, and that it would be directly translated into lowered morbidity and mortality rates. The Committee considered that not all relevant UK data were identified by the manufacturer's search strategy in the original submission, and that the manufacturer's response to the ACD addressed these concerns in part. The Committee acknowledged the changes to the model made by the manufacturer in their response to the ACD, but that substantial uncertainty remained about the long-term benefits of using mannitol. The Committee noted that the ICER would increase if the

effects of mannitol were only maintained in the short term. The Committee concluded that the cost-effectiveness model was complex and may not adequately reflect the clinical trial data.

- 4.15 The Committee considered the way in which the manufacturer had incorporated the clinical-effectiveness data in the model, and was concerned by the limited number of variables incorporated from the trials. It noted that the modelling of treatment effect used FEV<sub>1</sub>% predicted, and not the trials' primary outcomes of absolute FEV<sub>1</sub>. The Committee considered the assumptions and variables incorporated into the manufacturer's model, one of which being that mortality depended only on FEV<sub>1</sub>% predicted, the presence or absence of *Burkholderia cepacia* infection, age and sex. The Committee was aware that other studies, including one using UK data, demonstrated a wider range of variables associated with mortality in cystic fibrosis than the variables in the BioGrid data used by the manufacturer. The Committee particularly noted that BMI was not included in the manufacturer's mortality calculations, whereas it was a parameter for other variables in the model, and had been identified in registry studies as an independent risk factor for death in cystic fibrosis. In addition, the Committee noted that the hazard ratio associated with *Burkholderia cepacia* infection was greater in the manufacturer's analysis than in multivariate survival analyses of UK and US registry data. The Committee noted that the manufacturer stated that mannitol did not affect the risk of infection with *Burkholderia cepacia* complex in the model. The Committee acknowledged that there was little evidence that mannitol would alter other factors associated with mortality, but concluded that the mortality rate in the manufacturer's model may not accurately reflect mortality in cystic fibrosis. The Committee considered that other validated models of cystic fibrosis mortality exist, and that the manufacturer's model was unlikely to accurately represent the cystic fibrosis population in the UK. The Committee concluded that the model underestimated the mortality rate, and that a higher mortality rate would increase the ICER.
- 4.16 The Committee expressed concerns about the assumption used in the model related to how change in FEV<sub>1</sub>% predicted is modelled over time derived from the BioGrid study, but was satisfied with the manufacturer's clarification at the second meeting that FEV<sub>1</sub>% predicted declined over

time in the model, as expected in a cohort of patients with cystic fibrosis. Given that there is a rise in the rate of pulmonary exacerbations with age, the Committee considered it was difficult to interpret with any certainty the evidence provided by the regression model. The Committee was also concerned that the manufacturer did not consider the effect of treatment with mannitol on BMI, even though BMI was a parameter in the model used to estimate FEV<sub>1</sub>% predicted. The Committee concluded that there was substantial uncertainty in the assumptions surrounding the changes in FEV<sub>1</sub>% predicted with age and that this led to uncertainty about the applicability of the model to the UK population with cystic fibrosis.

- 4.17 The Committee considered the assumption that the difference in FEV<sub>1</sub>% predicted from treatment with mannitol observed at week 26 would be maintained over the patient's lifetime, and whether this was likely to be seen in clinical practice. The Committee noted that this delay in FEV<sub>1</sub> decline would prolong the time before, but possibly not prevent, future lung transplants. The Committee noted that the assumption of a maintained long-term benefit of mannitol would affect the ICER favourably, but that there was substantial uncertainty around this assumption. The Committee noted the sensitivity analyses carried out by the manufacturer and the ERG in which the time horizon was shortened to 5 and 10 years, which could be used as a proxy for a shorter duration of benefit, and that the ICERs were considerably increased with these shorter time horizons. However, it noted the ERG's opinion that a longer time horizon of 50 years may reflect the expected benefit of patients who entered the clinical studies with a mean age around 30 years. The Committee concluded that although there was evidence on the short-term effectiveness of mannitol on FEV<sub>1</sub>, the long-term effect of mannitol on FEV<sub>1</sub> was unknown and that this increased the uncertainty in the ICER.
- 4.18 The Committee considered the effect of varying adherence to treatment and of stopping rules on the ICERs, and discussed the ERG's sensitivity analysis and the manufacturer's revised analysis of reduced adherence. The Committee noted that, in the trial, the adherence was 87% based on the date of the last treatment, but the manufacturer had assumed costs reflecting 100% adherence in the model. The Committee therefore concluded that the costs of mannitol were overestimated in the original

submission. However, the Committee noted that the sensitivity analyses reported in the manufacturer's response to the ACD lacked face validity because the analyses included reduced costs for mannitol, but no changes to the benefits. The Committee concluded that there is uncertainty around the validity of the assumptions around adherence and whether stopping rules reflect clinical practice, but that an adherence rate as seen in the trial might reduce the base-case ICER.

- 4.19 The Committee noted from the manufacturer's comments that the original definition of PDPE, as used in the trials, was different from the definition used in clinical practice, and therefore more clinical exacerbations would be seen in clinical practice. The Committee considered that this could imply that mannitol may be more effective in preventing exacerbations and hospital admissions than assumed in the cost-effectiveness model, which used the trial definition of PDPE. The Committee concluded that, in clinical practice, mannitol could prevent more exacerbations than those within the PDPE definition, which would decrease the ICER.
- 4.20 The Committee considered that adverse reactions were not incorporated into the manufacturer's model. The Committee heard from the patient expert and clinical specialists that quality-of-life measurements did not accurately capture the effect of adverse reactions on the quality of life of people with cystic fibrosis. The Committee noted that treatments for cystic fibrosis can increase the incidence of haemoptysis, but that haemoptysis was also associated with exacerbations, which occurred less frequently in people taking mannitol compared with people not taking mannitol. The Committee concluded that the economic model had not incorporated the specific impact of adverse reactions on the health-related quality of life in people with cystic fibrosis and that there was uncertainty about how this would affect the ICER.
- 4.21 The Committee considered the generalisability and internal validity of the model. The Committee considered that the relationship between FEV<sub>1</sub>% predicted and lung transplantation in the model could not be fully explained by the manufacturer or the ERG. The Committee heard from the ERG that the proportion of people with cystic fibrosis alive at 55 years predicted by the model (15%) was greater than that found in the

UK cystic fibrosis population. The Committee heard from the ERG that approximately 2% of people with cystic fibrosis are still alive at 50 years, but the clinical specialists questioned the validity of this number from the cystic fibrosis registry data. The Committee noted the comparison of the Australian data with UK registry data provided by the manufacturer in response to the ACD, and the manufacturer's interpretation that this indicated a similar trend in mortality. The Committee noted that there was a difference between the mean FEV<sub>1</sub>% predicted values in the BioGrid and UK population datasets (see section 3.54). The Committee considered the clinical specialists' and ERG's comments that any improvement in FEV<sub>1</sub>% predicted would reduce the mortality rate. Based on this, the Committee was not persuaded by the manufacturer's interpretation, and remained concerned that mortality was not modelled in a way that accurately reflected the mortality rate in people with cystic fibrosis in the UK. The Committee noted that, when the relative risk of death for the individual subgroups was used in the model, more QALYs were gained with mannitol in people not using rhDNase than in people using rhDNase. The Committee heard from the manufacturer that this was possibly a chance finding because of the small sample size in the subgroup of people who could not use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The Committee concluded that there were substantial issues with generalisability and internal validity of the model, and that this would increase the uncertainty around the ICERs.

- 4.22 The Committee considered the quality-of-life measurements collected in the 2 trials and those used in the model. The Committee noted that the manufacturer had used the HUI2 utility measure, rather than the EQ-5D measure preferred by NICE. The Committee noted that the multiple comorbidities associated with cystic fibrosis and their large impact on daily life suggested that the baseline utility value of 0.899 was high, and that the revised figure of 0.896 for people not using rhDNase was not substantially different. The Committee was also aware that the model was sensitive to the baseline utility with the ICER increasing as the baseline utility decreased. In the original model, the utility increase in patients with improved respiratory symptoms was greater in the mannitol group than in the control group, whereas the utility decrease in patients without improved symptoms was greater in the control group than in the

mannitol group. In response to the ACD, the manufacturer submitted a model where the utility values for the health states were the same, irrespective of treatment. However, the Committee concluded that it was not convinced that the health-related quality of life of the health states in the model had been valued with any certainty, and that this led to increased uncertainty around the calculated ICERs for mannitol compared with best standard of care.

- 4.23 The Committee considered the relationship between the outcomes, mortality, and quality of life within the model. The Committee noted the uncertainty around the effect of mannitol on life expectancy given the assumption of lifetime efficacy in the model. The Committee noted that virtually all of the benefit of mannitol was from its modelled extension of life-years gained, with very little benefit resulting from improved health-related quality of life, and that the ERG suggested that a more direct link between lung function and quality-of-life utilities could have produced lower ICERs. The Committee considered whether this was likely to be an accurate reflection of real life, and heard from the patient expert that there were substantial quality-of-life improvements in taking an inhaled treatment such as mannitol. The Committee concluded that there was uncertainty about the accuracy of the quality-of-life data and the projected benefits of mannitol on life expectancy, and as a consequence there was further uncertainty as to the robustness of the modelled ICERs.
- 4.24 The Committee noted that the costs presented initially by the manufacturer were treatment specific rather than health-state specific. The Committee agreed that the use of health-state specific costs was more appropriate and acknowledged that the manufacturer had incorporated health-state specific costs in the model provided as part of the manufacturer's response to the ACD. The Committee concluded that the modelling incorporating health-state specific costs was more appropriate than that based on treatment specific costs, but that a model based on lung-function specific costs and utilities would be even more appropriate.
- 4.25 The Committee considered the ICERs produced by the manufacturer and the ERG. The Committee noted that the manufacturer's original base-



case ICERs were above £40,000 per QALY gained in both people using and people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. Furthermore, the Committee noted that the ERG's base-case ICERs were £82,500 per QALY gained in people using rhDNase and £29,900 per QALY gained in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, when subgroup specific model inputs were used. The Committee noted that, in response to a request for clarification, the manufacturer's probabilistic ICERs were £27,700 per QALY gained for people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and £54,300 per QALY gained in people using rhDNase, and the respective ERG's estimates were £30,100 per QALY gained for those who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and £53,800 per QALY gained for the rhDNase group. The Committee had not been provided with an ICER for the whole population for which mannitol is licensed, but could conclude from the subgroup data by rhDNase use that mannitol would not represent a cost-effective treatment for the whole population for which it is licensed. Noting that the ICERs for the subgroup of people using rhDNase were between £50,000 and £80,000 per QALY gained, the Committee concluded that mannitol was not cost effective for people using rhDNase, and could not be recommended for this subgroup. The Committee concluded that the ICERs for mannitol in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase were underestimates because mortality in the model was underestimated, and also associated with several uncertainties because of the lack of validity in the model (for example, the duration of the effect long term). Therefore, the Committee concluded that the ICERs for mannitol were likely to be above £30,000 per QALY gained in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and that mannitol could not be recommended for this subgroup.

- 4.26 The Committee was aware of the ICERs provided in the manufacturer's response to the ACD in the subgroup of people not using rhDNase (irrespective of the reason for not using rhDNase). The Committee understood from the ERG's critique that this new ICER in people not using rhDNase was lower than the ICER in the original subgroup of

people who cannot use rhDNase. According to the ERG there were several factors that could have led to the lower new ICER for adults not using rhDNase, including the manufacturer having used a bigger difference in cost between mannitol and control, having used exacerbation rates suggested by the ERG, and having included drop-out rates derived from the trials, rather than having assumed that all people whose condition responded to mannitol remained on treatment for their lifetime. However the Committee was also aware that mannitol improved lung function less in the people not using rhDNase than in people who cannot use rhDNase, and therefore found the new ICERs counterintuitive. Importantly, the Committee noted that the subgroup of people not using rhDNase (for unspecified reasons) is clinically not clearly identifiable, and therefore it could not make recommendations for this subgroup.

- 4.27 The Committee further explored whether there was a group of adults with cystic fibrosis in whom treatment with mannitol would provide a cost-effective use of NHS resources, taking into consideration the responses received on the ACD. The Committee was aware that the manufacturer had, in its response to the ACD, made a proposition for increased cost effectiveness for mannitol treatment in patients with rapidly declining lung function irrespective of rhDNase use. Furthermore, the Committee noted a statement from the clinical specialists in response to ACD consultation, which identified patients with rapidly declining lung function, despite best standard of care, because those patients would particularly benefit from mannitol, a suggestion that the Committee considered was biologically plausible. The Committee noted that any increase in lung function would be proportionally greater for patients with rapidly declining lung function because they would have more to gain than patients with more stable lung function. The Committee was therefore aware that a group with rapidly declining lung function has higher capacity to benefit from mannitol treatment. The Committee further noted that mannitol appeared to be more clinically effective in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase (see section 4.13). The Committee concluded that there is an unmet clinical need in patients with rapidly declining lung function, particularly if there are no other therapies appropriate to offer the patient.



- 4.28 The Committee discussed the cost effectiveness of mannitol in people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and whose lung function declines rapidly (yearly FEV<sub>1</sub>% predicted decline of more than 2%). The Committee used, as a starting point for these discussions, the manufacturer's original probabilistic ICER of £27,700 per QALY gained in people who cannot use rhDNase and the ERG's ICER of £30,100 per QALY gained. There were factors that the Committee agreed would increase uncertainty around the ICERs; those that may increase the ICERs include assumptions about mortality and the long-term effect of mannitol on lung function. Factors that may decrease the ICERs include the possibility of higher rates of pulmonary exacerbations in clinical practice, a rate of adherence reflecting clinical practice, establishing if there is a link between lung function and quality-of-life utilities, and estimating more realistic utility values associated with mannitol use. The Committee agreed that, if mannitol treatment was offered only to patients with a rapid decline in lung function, the ICER would most likely be lower because of this group's lower quality-of-life and lung function, and a greater potential to improve. The Committee concluded that the ICER for mannitol in patients for whom hypertonic saline is not considered appropriate (see section 4.10), who cannot use rhDNase, and whose lung function is rapidly declining would be under £30,000 per QALY gained. It also took into account the severity of the disease and the importance of treatment options for people with cystic fibrosis who have few alternative options. The Committee concluded that mannitol should be recommended as an acceptable use of NHS resources as a treatment option for people with cystic fibrosis who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, whose lung function is rapidly declining, and for whom other osmotic agents are considered inappropriate.
- 4.29 The Committee discussed whether mannitol should be considered an innovative technology, or if there were any significant and substantial health benefits that were not included in the economic model. It heard from the clinical specialists and the patient expert that the treatment burden is substantially less for an inhaler than for a nebuliser and that mannitol, being a dry powder, represents a step-change in the way cystic fibrosis is managed in the UK. When questioned, the manufacturer stated

that the model accurately reflected the utility gain to patients. The Committee concluded that treatment with an inhaler provided practical advantages over treatment with nebulisers, but mannitol as an add-on therapy would not replace the use of nebulisers, and so could not be considered a step-change in treatment.

- 4.30 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The only potential equality issue identified was whether the inhaler used for mannitol inhalation would present a disproportionate burden on patients with physical disabilities. However, the Committee noted the clinical specialists' and patient expert's view that all available treatments are difficult to administer, and that the use mannitol as an add-on therapy to best standard of care would not increase the treatment burden.

## Summary of Appraisal Committee's key conclusions

TA266	Appraisal title: Mannitol dry powder for inhalation for treating cystic fibrosis	Section
<b>Key conclusion</b>		
Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:		1.1
The Committee had not been provided with an ICER for the whole population for which mannitol is licensed. The manufacturer made cases for other subgroups, some based on the anticipated, but later amended wording of the marketing authorisation, for example people using rhDNase or people who cannot use rhDNase. However, the Committee concluded that the ICERs for these subgroups were too high for mannitol to be an appropriate use of NHS resources.		4.25

<p>The Committee agreed that people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and whose lung function declined rapidly (yearly FEV<sub>1</sub>% predicted decline of more than 2%) have an unmet clinical need, particularly as there are no other therapies available, and an increased capacity to benefit from treatment with mannitol. Although no ICER was specifically presented for this subgroup, the Committee was able to infer from the other evidence that the ICER for mannitol in this subgroup would be under £30,000 per QALY gained.</p>		4.28
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from the patient expert and clinical specialists that current treatments are difficult to use and do not encourage adherence. The Committee concluded that cystic fibrosis and its management had a major impact on the quality of life of patients and their carers.</p>	4.4
<b>The technology</b>		
<p>Proposed benefits of the technology</p>	<p>The patient expert explained the difficulties in adhering to current treatments, and felt that using mannitol with an inhaler would be easier than using hypertonic saline with a nebuliser and would be likely to encourage adherence.</p>	4.4
<p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>However, the Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use of nebulisers in cystic fibrosis treatments.</p>	4.29

What is the position of the treatment in the pathway of care for the condition?	Clinical specialists explained that after treatment with rhDNase, a patient would be offered either mannitol or hypertonic saline. A treatment pathway survey provided in response to the ACD found that mannitol was unlikely to be used in most patients, and that it would be unlikely to replace hypertonic saline in people with stable cystic fibrosis.	4.3
Adverse reactions	Treatments for cystic fibrosis can increase the incidence of haemoptysis, but haemoptysis is also associated with exacerbations, which occurred less frequently in people taking mannitol compared with people not taking mannitol. The Committee concluded that the treatment of cystic fibrosis can cause a number of moderate and severe adverse reactions, and that it can be difficult to establish the effect of adverse reactions on health-related quality of life.	4.11, 4.20
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The evidence of clinical effectiveness was derived from 2 randomised multinational double-blind controlled trials (DPM-CF-301 and DPM-CF-302). The trials were designed to assess the effectiveness of twice-daily mannitol at a dose of 400 mg compared with mannitol at a sub-therapeutic dose of 50 mg in addition to best supportive care with or without rhDNase. The trials had 26-week double-blind phases, followed by an unblinded phase of 26–52 weeks. The inclusion and exclusion criteria for the 2 trials were similar. Dividing the adult-only intention-to-treat population of 341 into users and non-users of rhDNase, and then into different populations of non-users of rhDNase further reduced the statistical power of the analyses.	3.1, 3.2, 3.3, 4.6
Relevance to general clinical practice in the NHS	The Committee heard from the clinical specialists that best standard of care for cystic fibrosis has a complex treatment pathway, that approximately 98% of patients with cystic fibrosis are registered with cystic fibrosis centres, and that clinicians use the Cystic Fibrosis Trust guidelines as the basis for best standard of care on an individual basis.	4.2

Uncertainties generated by the evidence	The Committee noted that there were significant concerns about the post-hoc stratification into subgroups by rhDNase use and lung function. It noted that the analysis was underpowered and the small numbers in these analyses increased uncertainty and reduced the statistical power of the trial results. The Committee noted that hypertonic saline was not presented as a comparator, and that mannitol would be unlikely to replace hypertonic saline in people with stable cystic fibrosis.	4.3, 4.5, 4.6, 4.8, 4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The manufacturer provided data for people using rhDNase, and people who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase. The Committee concluded that people who cannot use rhDNase may experience greater benefit from mannitol, but that there is a degree of uncertainty about the magnitude of any increased clinical effectiveness.	4.13
	Furthermore, data for people not using rhDNase (irrespective of the reason) were also provided as part of the manufacturer's response to the ACD. The Committee noted that the subgroup of people not using rhDNase (for unspecified reasons) is clinically not clearly identifiable, and therefore it could not make recommendations for this subgroup.	4.26
	The Committee also considered a subgroup of people with rapidly declining lung function (of greater than 2% per year). The Committee was aware that a group with rapidly declining lung function has higher capacity to benefit from mannitol treatment.	4.27
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that mannitol is clinically effective in improving both lung function (FEV <sub>1</sub> ) and pulmonary exacerbations in people with cystic fibrosis. The Committee further concluded that there are subgroups of people who may experience greater benefit from mannitol, such as people who cannot use rhDNase, but that there is a degree of uncertainty about the magnitude of any increased clinical effectiveness.	4.13

<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	<p>The manufacturer developed a Markov health-state transition model, taking into account individual patient pathways over a lifetime horizon, and modelling 2 treatment options: treatment with inhaled mannitol and treatment without inhaled mannitol. The manufacturer did include hypertonic saline as a comparator. The manufacturer did not use clinical-effectiveness data from the trials presented in the submission other than to obtain baseline values and some transition parameters; instead, the manufacturer derived transition parameters from the literature and from its own commissioned studies, incorporating them into the model using regression analysis. The Committee noted that the structure of the original model was not a health-state model, but rather was a model of the cystic fibrosis treatment pathway. The Committee acknowledged the changes to the model made by the manufacturer in their response to the ACD, in light of the ERG's concerns. The Committee concluded that the cost-effectiveness model was complex and may not adequately reflect the clinical trial data.</p>	3.18, 3.20, 4.14
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee was concerned about the manufacturer's assumptions that any improvement in FEV<sub>1</sub> would be maintained throughout the lifetime of the patient, and that it would be directly translated into lower morbidity and mortality rates. It was concerned about the limited number of variables incorporated into the model, and that there were other models of cystic fibrosis that had incorporated a greater variety of variables. The Committee concluded that there was substantial uncertainty surrounding the assumption that FEV<sub>1</sub>% predicted changed with age and that the use of UK data would have been more appropriate, and that this led to uncertainty about the applicability of the model to the UK population with cystic fibrosis.</p>	4.14, 4.15, 4.16, 4.17

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee was also aware that the model was sensitive to the baseline utility, with the ICER increasing as the baseline utility decreased. The Committee noted that adverse events and their effect on quality of life were not incorporated into the model. The Committee was concerned by the use of HUI2 data rather than the EQ-5D. The Committee concluded that it was not convinced that the health-related quality-of-life of patients with cystic fibrosis had been valued with any certainty. The Committee noted that virtually all of the benefit of mannitol was from its modelled extension of life years gained, with very little benefit resulting from improved health-related quality of life.</p>	<p>4.20, 4.22</p>
	<p>The Committee agreed with the manufacturer's statement at the meeting that the model included all potential benefits associated with mannitol treatment, and that no additional health-related benefits had been identified that had not been adequately captured by the economic model.</p>	<p>4.29</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee considered the subgroup defined by rapidly declining lung function (greater than 2% per annum) whose condition was unsuitable for treatment with rhDNase. The Committee noted that any increase in lung function would be proportionally greater, and that mannitol was likely to be more clinically effective in this subgroup, which would consequently decrease the ICER.</p>	<p>4.27, 4.28</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>Factors that would increase the ICERs include alternative assumptions about mortality and the long-term effect of mannitol on lung function. Factors that could decrease the ICERs included the possibility of higher rates of pulmonary exacerbations seen in clinical practice, a rate of compliance reflecting the trials, establishing if there is a link between lung function and quality-of-life utilities, and estimating more realistic utilities associated with mannitol use.</p>	<p>4.28</p>



Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that if mannitol treatment was offered only to patients with a rapid decline in lung function, the ICER would most likely be lower than in the whole population because of this group's lower quality of life and lung function, and a greater potential to improve. The Committee concluded that the ICER for mannitol in patients for whom hypertonic saline is not considered appropriate, who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and whose lung function is rapidly declining would be under £30,000 per QALY gained. It also took into account the severity of the disease and the importance of treatment options for people with cystic fibrosis who have few alternative options. The Committee concluded that mannitol should be recommended as an acceptable use of NHS resources as a treatment option in this group.	4.28
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable	
End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	The only potential equality issue identified was whether the inhaler used for mannitol inhalation would present a disproportionate burden on patients with physical disabilities. However, the Committee noted the clinical specialists' and patient expert's view that all available treatments are difficult to administer, and that the use mannitol as an add-on therapy to best standard of care would not increase the treatment burden.	4.30

## 5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 The technology in this appraisal may not be the only treatment for cystic fibrosis. If a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with section 5.1) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- A costing statement explaining the resource impact of this guidance.

## 6 Recommendations for further research

- 6.1 The Committee concluded that a clinical trial is needed to establish the relative effectiveness of mannitol compared with hypertonic saline.

## 7 Related NICE guidance

7.1 There is no related guidance for this technology.

## 8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in October 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon  
Chief Executive  
November 2012

# Appendix A: Appraisal Committee members and NICE project team

## A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital

### **Professor Ken Stein (Vice Chair)**

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

### **Professor Keith Abrams**

Professor of Medical Statistics, University of Leicester

### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University

of Oxford

**Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor John Cairns**

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

**Mark Chapman**

Health Economics and Market Access Manager, Medtronic UK

**Eleanor Grey**

Lay member

**Dr Neil Iosson**

General Practitioner

**Anne Joshua**

Associate Director of Pharmacy, NHS Direct London

**Terence Lewis**

Lay Member

**Professor Ruairidh Milne**

Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

**Dr Rubin Minhas**

General Practitioner and Clinical Director, BMJ Evidence Centre

**Dr Elizabeth Murray**

Reader in Primary Care, University College London

**Dr Peter Norrie**

Principal Lecturer in Nursing, De Montfort University



**Professor Stephen Palmer**

Professor of Health Economics, Centre for Health Economics, University of York

**Dr Sanjeev Patel**

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr John Rodriguez**

Assistant Director of Public Health, NHS Eastern and Coastal Kent

**Alun Roebuck**

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Navin Sewak**

Primary Care Pharmacist, NHS Hammersmith and Fulham

**Roderick Smith**

Finance Director, West Kent Primary Care Trust

**Cliff Snelling**

Lay Member

**Marta Soares**

Research Fellow, Centre for Health Economics, University of York

**Professor Rod Taylor**

Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

**Tom Wilson**

Director of Contracting & Performance, NHS Tameside & Glossop

**Dr Nerys Woolacott**

Senior Research Fellow, Centre for Health Economics, University of York

## **B NICE project team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Dr Grace Jennings**

Technical Lead

### **Dr Pall Jonsson and Dr Bhash Naidoo**

Technical Advisers

### **Jeremy Powell**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

- Riemsma R, Maiwenn J et al. Mannitol dry powder for inhalation for the treatment of cystic fibrosis, Kleijnen Systematic Reviews (April 2011).

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Pharmaxis

II Professional/specialist and patient/carer groups:

- Association of Respiratory Nurse Specialists
- British Thoracic Society
- Cystic Fibrosis Trust
- Royal College of Nursing
- Royal College of Paediatrics & Child Health
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III Other consultees:

- Department of Health

- Sandwell PCT
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Roche Products

C The following individuals were selected from clinical specialists and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on mannitol by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mrs Penny Agent, Deputy Director of Rehabilitation & Therapies, Royal Brompton & Harefield HS Foundation Trust, nominated by Pharmaxis – clinical specialist
- Dr Diana Bilton, Consultant Physician, Royal Brompton Hospital, nominated by Pharmaxis – clinical specialist
- Mrs Emma Lake, Senior Clinical Care Patient Advisor, the Cystic Fibrosis Trust, nominated by the Cystic Fibrosis Trust – patient expert

D The following individuals were nominated as NHS Commissioning experts by the selected PCT allocated to this appraisal. They gave their expert/NHS commissioning personal view on mannitol by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Alexis Macherianakis, Consultant in Public Health Medicine, Sandwell PCT, selected by Sandwell PCT – NHS Commissioning expert

E Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific

issues and comment on factual accuracy.

- Pharmaxis

# Changes after publication

**February 2014:** minor maintenance

# About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

## Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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