NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The therapeutic indication for mannitol in the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) has changed from the original submission. The CHMP now recommends the granting of a marketing authorisation for mannitol for the treatment of cystic fibrosis in adults as an add-on therapy to best standard of care. This is broader than the original marketing authorisation sought, which was for mannitol for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to rhDNase, and in patients ineligible, intolerant, or with an inadequate response to rhDNase. What is the Committee's view on how the evidence submitted for this technology appraisal addresses the updated marketing authorisation (see section 3.1)?
- In the Committee's view does the heterogeneity of best supportive care for cystic fibrosis in the clinical trials reflect UK best practice?
- The manufacturer's submission contained evidence which combined patients not receiving rhDNase into one category, 'rhDNase non-users'. After a request from the ERG for clarification from the ERG, these data

were divided into ‘rhDNase ineligible, intolerant or inadequately responsive’, ‘rhDNase suitable’ and ‘unknown reason for non-use’. What is the Committee’s view on the robustness of the evidence given the post-hoc stratification employed in the manufacturer’s submission and in the ERG report?

- In the Committee’s view was the trial adequately powered to detect differences between the subgroups (rhDNase users ‘rhDNase unsuitable’ non-users, and the adult population) in the DPM-CF-301 and DPM-CF-302 trials?
- What is the Committee’s view on the robustness of the evidence given that only changes in lung function and pulmonary exacerbations were reported for the relevant subgroups? Did the end points reflect clinical practice?
- What is the Committee’s view on the lack of hypertonic saline as a comparator in the manufacturer’s submission? The ERG performed an analysis based on the best available data, but emphasised that this analysis was not methodologically robust.

Cost effectiveness

- The ERG and the manufacturer differed on the division of the populations for economic analysis. The manufacturer’s submission compared mannitol with mannitol plus rhDNase, suggesting in the clarification document that the effectiveness of mannitol is independent of the concomitant use of rhDNase. The ERG interpreted this differently, suggesting that this analysis implied that best supportive care was equivalent in effectiveness to best supportive care with rhDNase. The ERG performed a different set of analyses: one comparing mannitol plus rhDNase against best supportive care plus rhDNAse for patients who can receive rhDNase, and the other comparing mannitol against best supportive care for patients who cannot receive rhDNase. These differing divisions of the population had a large effect on the incremental cost-effectiveness ratios (ICERs) calculated. What is the Committee’s view on the effect of this stratification on the cost effectiveness of mannitol?

- The variables used in the model for determining decline in FEV_1% predicted were age and pulmonary exacerbations, and the parameters in the model for mortality were FEV1% predicted decline and *Burkholderia cepacia* complex infection. What is the Committee's view on the use of only these parameters as the basis for the economic model, and the use of trial data within regression equations in the model rather than the use of the reported clinical outcomes?
- What is the Committee's view on the evidence presented of the link between measured FEV_1, mortality and health-related quality of life? What effect does an improvement in FEV_1 have on mortality and health-related quality of life?
- What is the Committee's view on the use of HUI2 data from DPM-CF-302 to derive health-related quality of life utilities, and on the use of treatment specific health-related quality of life derived utilities and costs rather than health-state specific utilities and costs?
- The manufacturer did not include several types of adverse reaction in their quality of life calculations, including cough and haemoptysis. In the Committee's view what effect does this have on the cost-effectiveness results?
- What are the Committee's views on the adherence and drop-out rates for mannitol use given by the manufacturer and the effect of these on the cost effectiveness of mannitol?
- What is the Committee's view on the assumption that FEV_1 improvement would be sustained over the lifetime of the patient and the assumption that patients would remain on mannitol for life?

1 Background: Clinical need and practice

1.1 Cystic fibrosis is caused by the inheritance of two copies of a recessive allele for the *CFTR* gene. This leads to faulty transport of sodium and calcium across cell membranes and viscous secretions in the lungs, pancreas, liver and reproductive organs. Much of the

morbidity and mortality in cystic fibrosis results from obstruction of the lungs by these viscous secretions and colonisation by pathogenic bacteria. Chronic inflammation leads to permanent lung damage, and often to respiratory failure, which may necessitate lung transplantation. Other problems associated with cystic fibrosis include prolonged diarrhoea, diabetes, and the inability to gain and maintain weight. Cystic fibrosis is usually diagnosed in the perinatal period, and disease progression is monitored by regular visits to the GP and to specialist CF centres.

1.2 Mutations in the *CFTR* gene are carried by 1 in 25 of the white population, and lead to cystic fibrosis in 1 in 2500 live births. In 2006 approximately 270 babies were born with cystic fibrosis in England and Wales, and there are approximately 9000 people living with cystic fibrosis in the UK.

1.3 People with cystic fibrosis have a life expectancy of approximately 38 years, but in 2009 more than half of the people with cystic fibrosis in the UK were older than 16 years.

1.4 There is no cure for cystic fibrosis; the aim of treatment is to improve quality of life and increase life expectancy. The care given to patients with cystic fibrosis varies according to individual needs and the specialist centre. The Cystic Fibrosis Trust's standards for the clinical care of children and adults with cystic fibrosis recommends prompt diagnosis, regular follow-up from a specialist cystic fibrosis centre and a multidisciplinary team experienced in the care of people with cystic fibrosis, prevention of pulmonary cross-infections, use of antibiotics for both prophylaxis and treatment of acute and chronic infections, twice-daily physiotherapy, nutritional support, identification of other complications (especially liver disease and impaired glucose

metabolism), psychosocial support, and long-term planning for the transition to adult care and for end-of-life and palliative care. Treatment for the pulmonary complications of cystic fibrosis includes a combination of physiotherapy, bronchodilators, inhaled mucolytics (such as rhDNase), inhaled and intravenous antibiotics, and anti-inflammatories. Treatment is also given for pancreatic and gastrointestinal complications. Best supportive care includes physiotherapy at least twice a day, prophylactic antibiotics, pancreatic enzymes, dietary support, and ongoing supervision.

1.5 The use of mucolytics increases the risk of cough, haemoptysis and other adverse reactions. Mucolytics also represent an increased burden of treatment for a condition with time-consuming daily therapies.

2 The technology

2.1 Mannitol (Bronchitol, Pharmaxis) is a mucoactive agent that causes water to enter the airway lumen so improving hydration of airway secretions. This increases the clearance of secretions and pathogenic bacteria by reducing the viscosity of secretions and stimulating cough. Mannitol dry powder is inhaled from a hand-held, breath-activated device. Mannitol has received a positive opinion from the CHMP for the treatment of cystic fibrosis in adults as an add-on therapy to best standard of care, but has not yet been granted full marketing authorisation. The dose used in clinical trials was 10 40-mg capsules inhaled twice daily, giving a cumulative dose of 400 mg twice daily.

2.2 The most common adverse reactions associated with mannitol were cough, CF exacerbation, headache and pharyngolaryngeal pain. The most clinically significant adverse event associated with mannitol use was haemoptysis. The summary of product

characteristics lists the following adverse reactions for mannitol: bronchospasm, cough, pharyngolaryngeal pain, headache, dizziness, eye pruritus, rhinorrhoea, throat irritation, aggravated asthma, dypsnoea, nausea, upper abdominal pain, diarrhoea, vomiting, back pain, nasopharyngitis, upper respiratory tract infection, fatigue and chest tightness. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price indicated in the manufacturer's submission is £0.84 per 40-mg capsule, or an average cost of £16.88 per day, including the cost of the inhaler. The manufacturer's submission quoted a cost for a 14-day pack of 280 capsules and two inhalers as £236.25. These prices do not include VAT. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of mannitol dry powder for inhalation within its licensed indication for the treatment of cystic fibrosis.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with cystic fibrosis	Adults (18 years and above) with cystic fibrosis

The manufacturer restricted the submission to adults of 18 years and above because this is the current indication. The Evidence Review Group (ERG) agreed that this was appropriate.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Mannitol dry powder for inhalation	Mannitol dry powder for inhalation. Mannitol is given in addition to best supportive care with or without rhDNase

The manufacturer altered the submission to indicate that the placement in the treatment pathway sought for mannitol was as an add-on therapy. The ERG did not query this.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	The following treatments used alone or in combination with each other: • inhaled mucolytics: rhDNase • nebulised hypertonic saline • best supportive care (which may include a wide range of inhaled and oral active treatments)	The following comparators will be evaluated: • rhDNase plus best supportive care • best supportive care • nebulised hypertonic saline

There were differences between the comparators defined in the scope and those addressed in the decision problem. rhDNase was not included as a comparator because all patients randomised to the mannitol arm of the trial received either rhDNase therapy plus mannitol, or mannitol alone (if they were ineligible, intolerant or inadequately responsive to rhDNase). This was not disputed by the ERG. There was discussion that this then created two groups for comparison, mannitol in rhDNase users and in non-users who were ineligible, intolerant or inadequately responsive to rhDNase. Best supportive care was a very broad category because treatment must be tailored to individual needs. In the trials, best supportive care involved multiple treatments, with few limitations on the co-medications permitted. Best supportive care often included inhaled antibiotics, anti-inflammatory agents, bronchodilators, agents that assist in mucus clearance, vitamin supplements, pancreatic enzymes and anti-diabetic agents.

The ERG highlighted that hypertonic saline was not included as a comparator by the manufacturer. The manufacturer stated that this was because of the

heterogeneity of the respective studies and the lack of a common control group between studies. The ERG conducted its own analysis of the best available evidence on hypertonic saline as a comparator to mannitol.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	The outcome measures to be considered include: • mortality • lung function • respiratory symptoms • reduction in pulmonary exacerbations • exercise tolerance • adverse effects of treatment • health-related quality of life	The following outcomes will be included: • mortality • lung function (decline in percentage predicted FEV_1) • improvement in respiratory symptoms (respiratory domain CFQ-R) • rate of pulmonary exacerbations needing hospitalisation • improvement in exercise tolerance (physical domain CFQ-R) • adverse effects of treatment • health-related quality of life

The ERG highlighted several issues with the outcome data provided by the manufacturer. In particular, mortality data were not assessed in any population in the trials, and no data were provided on mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life in the relevant subgroups.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Economic evaluation	NICE reference case with costs considered from an NHS and personal social services perspective. Resource use should take account of any reduction in pulmonary exacerbations in both the primary and secondary care settings.	NICE reference case with a life-long time horizon and costs considered from an NHS and personal social services perspective. Resource use will be taken from the hospitalisations, hospital visits, community health care visits and CF-related concomitant medication collected in the DPM-CF-301 and DPM-CF-302 trials.

There was no difference in the economic approach used in the manufacturer's submission from that proposed in the scope.

3.2 Mannitol is proposed as an add-on therapy, to be used in combination with any other treatments currently used for cystic fibrosis.

4 Clinical-effectiveness evidence

4.1 The manufacturer presented clinical effectiveness data from two randomised control trials (DPM-CF-301 and DPM-CF-302). These were large-scale multi-national, multi-centre clinical trials. The trials were designed to assess the incremental effectiveness of twice-daily mannitol at a dose of 400 mg in addition to best supportive care with or without rhDNase. Best supportive care often included inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for patients with diabetes. The trials had 26-week double-blind phases, followed by an unblinded phase of 26–52 weeks. The inclusion and exclusion criteria for the two trials were comparable. DPM-CF-301 had 295 participants with 190 adult participants and took place at 40 centres in Australia, New Zealand, the UK and Ireland. DPM-CF-302 had 305 participants (151 adult participants) and took place at 53 centres in the USA, Canada, Argentina, Germany, Belgium, France and The Netherlands. The numbers of patients according to intervention and subgroup are given in table 1.

Table 1 Numbers of participants in the DPM-CF-301 and 302 trials according to intervention and subgroup (taken from table 11 of the ERG report)

	DPM-CF-301			**DPM-CF-302**		
	Mannitol	Control	Total	Mannitol	Control	Total
Total	177	118	295	184	121	305
Adults	114	76	190	93	58	151
rhDNase group	96	67	163	137	92	229
Adult rhDNase group	58	44	102	64	41	105
Adults ineligible for rhDNase	30	13	43	15	7	22

4.2 The trial protocols for DPM-CF-301 and DPM-CF-302 were very similar. Potential participants were initially screened for bronchial hyper-responsiveness to mannitol, and those with hyper-responsiveness were excluded from study. Eligible patients were then randomised to receive either 400 mg mannitol twice daily, or a placebo sub-clinical dose of 50 mg mannitol twice daily (the minimum dose available to preserve blinding in physicians and patients). There were four follow-up visits after the screening visit, at week 0 (to start treatment with control or mannitol) and at weeks 6, 14, and 26. In the DPM-CF-302 trial, patients were offered the opportunity to continue or start mannitol treatment in an open-label phase for a further 26 weeks, an open-label extension phase was also offered in order to gain further safety information. Compliance was measured by the number of blister packs returned at each visit. Protocol compliance was defined as less than 20% medication returned at each visit.

4.3 The primary outcome measured in both trials was the forced expiratory volume at 1 second (FEV_1), which is considered to be a good indicator of the progression of chronic obstructive pulmonary diseases (including cystic fibrosis). Both trials reported changes in

FEV_1 from baseline in the mannitol group compared with the control.

4.4 Secondary outcomes included FEV_1 responders defined as those achieving at least 100 ml increase in FEV_1 from baseline, at least 5% relative increase in FEV_1 from baseline, or at least 5% increase in 'predicted FEV_1%' (defined as the FEV_1 of the patient divided by the mean FEV_1 in the population for a person of similar age, sex and body composition, with population values as calculated in appendix 17 of the manufacturer's submission). Protocol-defined pulmonary exacerbations (PDPE) were defined as pulmonary events needing antibiotic treatment for four or more signs and/or symptoms. Reductions in both PDPE and hospital care were measured in both studies.

4.5 Quality of life was measured by the Cystic Fibrosis Questionnaire – Revised (CFQ-R) in both trials, and by the Health Utility Index (HUI) in DPM-CF-302. The CFQ-R was administered before the start of the trials, and then at weeks 14 and 26. There is no total score for the CFQ-R as there is for the HUI. In order to measure improvement in respiratory symptoms, the manufacturer's submission defined the minimal clinically important difference in the CFQ-R score as 4.0, which equated to approximately one category change for one question. Reduction of antibiotic use and safety profile were also measured in both trials.

4.6 The therapeutic indication for mannitol in the CHMP positive opinion is as an add-on therapy to best standard of care in adult patients. However, the trial data were collected and analysed by the manufacturer for the originally proposed indication (that is, as an add-on therapy for adults receiving rhDNase, or for patients ineligible, intolerant, or inadequately responsive to rhDNase). The

ERG's exploratory analysis was also conducted for the originally proposed indication.

4.7 Participants in the DPM-CF-301 trial all had cystic fibrosis, were aged 6 years or older, had a predicted FEV_1 between 30% and 90%, had no concomitant hypertonic saline use, and had passed the mannitol tolerance test. The mean age was 23.1 years; 40.1% of the population was female and 95.5% of the population was white. In the adult-only population, the mean age was 29.6 years, 37.7% of the population was female and 97.4% of the trial population was white.

4.8 In the manufacturer's original submission only lung function was reported for one of the relevant subgroups, adult rhDNase users. Following clarification, data on change in FEV_1 and exacerbation were submitted for the adult rhDNase group and adults who are ineligible, intolerant or inadequately responsive to rhDNase. In the DPM-CF-301 trial, mannitol plus rhDNase statistically significantly improved lung function between 6 and 26 weeks in patients with cystic fibrosis compared with control, as measured by change in FEV_1 from baseline of 109.27 ml (95% confidence interval [CI] 52.77 to 165.77; $p < 0.001$). This difference was evident at 6 weeks and was maintained over the 26-week double-blind phase. The other measures for lung function in patients receiving mannitol plus rhDNase compared with control were: mean change in FEV_1 from baseline of 4.19% (95% CI 0.31 to 8.07); change in predicted FEV_1 of 2.66% (95% CI 0.59 to 4.73) and change in Forced Vital Capacity FVC of 117.42 ml (95% CI 1.00 to 233.85). FVC is the volume change of the lungs between a maximum inspiration to total lung capacity and a maximum expiration to residual volume. Following clarification, the change in FEV_1 between 6 and 26 weeks for the 43 patients receiving mannitol who are ineligible,

intolerant or inadequately responsive to rhDNase was 146.98 ml which was statistically significantly different from control (p=0.02 n=43).

4.9 PDPE incidence in the DPM-CF-301 trial was 27.59% for adults receiving mannitol plus rhDNase compared with 36.36% in the control population. For adults who are ineligible, intolerant or inadequately responsive to rhDNase, the incidence of PDPE was 16.67% for those receiving mannitol compared with 30.77% in the control population. The rate of PDPE per year was 1.42 (±2.69 standard deviation [SD]) for adults receiving mannitol plus rhDNase compared with 1.58 (±2.70 SD) in the control population, and 0.41(±1.11 SD) for adults who are ineligible, intolerant or inadequately responsive to rhDNase compared with 0.64 (±1.00 SD) in the control population. However, the trials were not powered to demonstrate statistically significant differences for these outcomes in these subgroups.

4.10 FEV_1 responder status in the DPM-CF-301 trial was not reported for the adult rhDNase group or for adults who are ineligible, intolerant or inadequately responsive to rhDNase.

4.11 Participants in the DPM-CF-302 trial all had cystic fibrosis, were aged 6 years or older, had a predicted FEV_1 between 40% and 90%, had no concomitant hypertonic saline use, and had passed the mannitol tolerance test. The mean age was 19.6 years, 48.9% of the population was female and 98.9% of the trial population was white. The mean age of the adult-only population was 24.0 years, with 29.8% female and 98.9% white.

4.12 In the DPM-CF-302 trial, the mean change in FEV_1 between 6 and 26 weeks for patients receiving mannitol plus rhDNase was not significantly different from controls (88.45 ml, 95% CI –8.46 to

185.36). For the other measures of lung function in patients receiving mannitol plus rhDNase, the mean changes from baseline were 5.43% (95% CI –0.44 to 11.31) for FEV_1, 2.95% (95% CI –0.61 to 6.50) for change in predicted FEV_1, and 96.94 ml (95% CI –7.68 to 201.55) for changes in FVC. Following clarification, change in FEV_1 between 6 and 26 weeks for mannitol in 22 patients who are ineligible, intolerant or inadequately responsive to rhDNase was 208.6 ml (p = 0.061).

4.13 PDPE incidence in the DPM-CF-302 trial was 9.76% for adults receiving mannitol plus rhDNase compared with 18.75% in the control population. For adults who are ineligible, intolerant or inadequately responsive to rhDNase, PDPE incidence was 13.33% for patients receiving mannitol compared with 42.86% in the control population. PDPE rate per year was 0.83 (±2.51 SD) for adults receiving mannitol plus rhDNase compared with 0.19 (±0.58 SD) in the control population, and 0.26 (±0.68 SD) for adults who are ineligible, intolerant or inadequately responsive to rhDNase compared with 0.86 (±1.08 SD) in the control population. However, the trials were not powered to demonstrate statistically significant differences for these outcomes in these subgroups.

4.14 In the DPM-CF-302 trial, FEV_1 responder status was not reported for adult rhDNase users, or for adults who are ineligible, intolerant or inadequately responsive to rhDNase.

4.15 The manufacturer's submission presented pooled analyses of the DPM-CF-301 and DPM-CF-302 trials. The end points in the pooled analysis were FEV_1% predicted, FEV1 responder, and per patient per year rate of PDPE in the adult population. However, only FEV_1% predicted was reported for one of the relevant populations, adult rhDNase users. Following clarification, results for change in

FEV1 and pulmonary exacerbation were submitted for adult rhDNase users and adults who are ineligible, intolerant or inadequately responsive to rhDNase. For the pooled adult population of rhDNase users, the mean change in FEV_1% between 6 and 26 weeks for patients receiving mannitol plus rhDNase was 94.06 ml (no 95% CI given), and patients receiving mannitol who are ineligible, intolerant or inadequately responsive to rhDNase 166.73 ml (95% CI not given).

4.16 PDPE incidence in the pooled population was 22.95% for adults receiving mannitol plus rhDNase compared with 23.53% controls. For adults who are ineligible, intolerant or inadequately responsive to rhDNase, the PDPE incidence was 15.56% for those receiving mannitol compared with 35.0% in controls. PDPE rate per year was 1.09 (±2.60 SD) for adults receiving mannitol plus rhDNase compared with 0.91 (±2.10 SD) in controls, and 0.36 (±0.91 SD) for adults who are ineligible, intolerant or inadequately responsive to rhDNase compared with 0.72 (±1.01 SD) in controls. The trials were not powered to demonstrate statistically significant differences for these outcomes in these subgroups.

4.17 For FEV_1 response in the adult population the manufacturer did not differentiate by rhDNase status, and did not submit a statistical analysis of the difference between the two groups (see table 2).

Table 2 FEV1 responders, in the adult only population: combined results from the DPM-CF-301 and DPM-CF-302 trials (taken from table 31 in the manufacturer's submission)

	Mannitol (n = 207)	**Control (n = 134)**
Baseline to week 26		
FEV_1 ≥ 100 ml	72 (34.8%)	30 (22.4%)
FEV_1 ≥ 5%	68 (32.9%)	30 (22.4%)
% predicted FEV_1 ≥ 5%	48 (23.2%)	19 (14.2%)
Baseline to week 6		
Combined responder at week 6[a]	100 (48.3%)	46 (34.3%)
a The combined response at week 6 included those with a relative increase of at least 5% in FEV_1 or an absolute increase in the FEV_1 of at least 100 ml.		

4.18 The manufacturer did not submit a comparison of mannitol with hypertonic saline, although the latter was included as a comparator in the scope. The manufacturer cited the heterogeneity of the studies as a barrier to undertaking an indirect comparison.

4.19 Adverse events were not reported for the rhDNase subgroups, but instead for the whole adult population. Overall, approximately 89% of all patients experienced at least one adverse event, with the most common adverse reaction being cough, which was the only adverse reaction in more than 10% of patients. The manufacturer stated that productive cough was a desired sequel of treatment with mannitol. Other adverse reactions with prevalence rates between 1% and 10% were decreased appetite, headache, haemoptysis, bronchospasm, wheezing, asthma, condition aggravated, pharyngolaryngeal pain, chest discomfort and bacteria sputum.

Table 3 Most common adverse events in the rhDNase and non-rhDNase groups in the DPM-CF-301 and DPM-CF-302 trials (taken from tables 46 and 47 of the manufacturer's submission

	DPM-CF-301		DPM-CF-302	
rhDNase group	**Mannitol (n = 96)**	**Control (n = 67)**	**Mannitol (n = 137)**	**Control (n = 92)**
Condition aggravated	36 (37.5%)	27 (40.3%)	63 (46.0%)	41 (44.6%)
Cough	31 (32.3%)	15 (22.4%)	24 (17.5%)	12 (13.0%)
Headache	21 (21.9%)	15 (22.4%)	20 (14.6%)	16 (17.4%)
Haemoptysis	13 (13.5%)	7 (10.4%)	12 (8.8%)	3 (3.3%)
Pharyngolaryngeal pain	17 (17.7%)	2 (3.0%)	12 (8.8%)	9 (9.8%)
Upper respiratory tract infection	6 (6.3%)	6 (9.0%)	9 (6.6%)	8 (8.7%)
Abdominal pain upper	7 (7.3%)	7 (10.4%)	9 (6.6%)	5 (5.4%)
Vomiting	9 (9.4%)	3 (4.5%)	8 (5.8%)	1 (1.1%)
Bacteria sputum identified	20 (20.8%)	11 (16.4%)	NR	NR
Nasopharyngitis	15 (15.6%)	9 (13.4%)	NR	NR
Lower respiratory tract infection	7 (7.3%)	11 (16.4%)	NR	NR
Productive cough	9 (9.4%)	5 (7.5%)	NR	NR
Arthralgia	7 (7.3%)	3 (4.5%)	NR	NR
Pyrexia	NR	NR	13 (9.5%)	10 (10.9%)
Pharyngitis	NR	NR	7 (5.1%)	2 (2.2%)
Sinusitis	NR	NR	7 (5.1%)	6 (6.5%)
Bronchitis	NR	NR	4 (2.9%)	5 (5.4%)
Fatigue	NR	NR	3 (2.2%)	5 (5.4%)
Non-rhDNase group	**Mannitol (n = 81)**	**Control (n = 51)**	**Mannitol (n = 47)**	**Control (n = 29)**
Condition aggravated	21 (25.9%)	15 (29.4%)	13 (27.7%)	13 (44.8%)
Cough	14 (17.3%)	9 (17.6%)	4 (8.5%)	4 (13.8%)
Headache	17 (21.0%)	13 (25.5%)	6 (12.8%)	6 (20.7%)
Nasopharyngitis	10 (12.3%)	8 (15.7%)	5 (10.6%)	2 (6.9%)
Pharyngolaryngeal pain	7 (8.6%)	3 (5.9%)	7 (14.9%)	4 (13.85)
Upper respiratory tract infection	8 (9.9%)	2 (3.9%)	1 (2.1%)	3 (10.3%)
Abdominal pain upper	5 (6.2%)	0	2 (4.3%)	3 (10.3%)

Bacteria sputum identified	13 (16.0%)	11 (21.6%)	NR	NR
Lower respiratory tract infection	8 (9.9%)	9 (17.6%)	NR	NR
Haemoptysis	8 (9.9%)	3 (5.9%)	NR	NR
Productive cough	3 (3.7%)	2 (3.9%)	NR	NR
Arthralgia	5 (6.2%)	4 (7.%8)	NR	NR
Vomiting	4 (4.9%)	1 (2.0%)	NR	NR
Abdominal pain	NR	NR	5 (10.6%)	3 (10.3%)
Pyrexia	NR	NR	4 (8.5%)	3 (10.3%)
Bronchitis	NR	NR	3 (6.4%)	0
Influenza	NR	NR	3 (6.4%)	2 (6.9%)
Influenza like illness	NR	NR	3 (6.4%)	0
Malaise	NR	NR	3 (6.4%)	0
Nasal congestion	NR	NR	3 (6.4%)	0
Pain in extremity	NR	NR	3 (6.4%)	1 (3.4%)
Diarrhoea	NR	NR	2 (4.3%)	2 (6.9%)
Toothache	NR	NR	2 (4.3%)	2 (6.9%)
Dizziness	NR	NR	0	2 (6.9%)
Gastrooesophageal reflux disease	NR	NR	0	2 (6.9%)
Procedural pain	NR	NR	0	2 (6.9%)
Stomach discomfort	NR	NR	0	2 (6.9%)
NR, not reported.				

4.20 The adverse event presented by the manufacturer as most significant clinically in both studies was haemoptysis. This was observed in 11.9% of patients receiving mannitol and 8.5% of patients in the control groups in the DPM-CF-301 trial, and in 7.1% and 2.5% respectively in the DPM-CF-302 trial. The drop-out rate in DPM-CF-301 was 36.7% over the initial 26 week period in the mannitol arm and 27.1% in the control arm. The drop-out rate in DPM-CF-302 was lower, with 16.8% over the initial 26 week period in the mannitol arm and 11.4% in the control arm. This drop-out rate includes all withdrawals post-randomisation.

4.21 Health-related quality of life was not reported for the rhDNase subgroups, but was reported for the whole adult population. There were no statistically significant changes in the CFQ-R domains in either trial for patients receiving mannitol (see table 4).

Table 4 Health-related quality of life in terms of CFQ-R outcomes for the DPM-CF-301 and DPM-302 trials (taken from table 22 of the manufacturer's submission)

Outcome	DPM-CF-301		DPM-CF-302	
	Mannitol (n = 177)	Control (n = 118)	Mannitol (n = 184)	Control (n = 121)
Respiratory domain of CFQ-R				
Change from baseline to week 26	1.3 (15.95)	-2.5 (17.55)	-1.4 (20.16)	5.6 (22.51)
Physical domain of CFQ-R				
Change from baseline to week 26	-0.5 (16.22)	-4.7 (17.56)	-1.7 (18.85)	1.1 (18.20)
Vitality domain of CFQ-R				
Change from baseline to week 26	2.1 (15.88)	-5.1 (18.13)	-1.6 (20.48)	-4.2 (17.72)

4.22 The results suggest 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 between patients receiving mannitol and controls in HUI measurements (mean baseline for mannitol was 0.896, SD 0.107, mean at visit 4 (week 26) for mannitol was 0.881, SD 0.133; mean baseline for control was 0.903, SD 0.094, mean at visit 4 (week 26) for control was 0.887, SD 0.121).

Evidence Review Group comments

4.23 The ERG regarded DPM-CF-301 and DPM-CF-302 as well designed, high-quality randomised controlled trials, with a large study population (total of 600 patients in both trials).

4.24 The ERG noted the change in therapeutic indication of mannitol to the adult population, which reduced the study population to a total of 341 over the two trials, and consequently greatly reduced the statistical power of all the analyses. The ERG also highlighted that the manufacturer had combined all those not taking rhDNase into one group, and had incorporated those not taking rhDNase for reasons other than incompatibility in the non-use group. The ERG noted that this was contrary to the anticipated marketing authorisation, and would be an inappropriate comparison group.

4.25 The ERG asked for clarification of the stratification of data for adults according to rhDNase use; clarification was particularly sought on adults ineligible, intolerant or inadequately responsive to rhDNase. The manufacturer provided this information for several measures, including incidence and rate of PDPE, and some data on FEV_1 change. However, the ERG noted that data were missing for several outcomes, and FEV_1 response was only presented as aggregated data, rather than using the different pre-defined definitions.

4.26 The ERG agreed with the findings of the manufacturer's submission regarding the change in FEV_1, change in FEV_1 %, predicted FEV_1, the incidence and rate per year of PDPE in the DPM-CF-301 and DPM-CF-302 trials.

4.27 The ERG was concerned that the manufacturer had not provided data on mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life (which were specified as outcomes in the scope) in the relevant populations. The manufacturer submitted information on PDPE incidence and PDPE rate per year, and the overall FEV_1 response for the two rhDNase subgroups defined in the scope (rhDNase users and adults

ineligible, intolerant or inadequately responsive to rhDNase), but did not submit data on the mortality rate, individual components of the FEV_1 response, respiratory symptoms, exercise tolerance, adverse events, or health-related quality of life measured by the CFQ-R for the two rhDNase subgroups, as outlined in the scope.

4.28 The ERG's pooled analyses showed statistical significance for all lung function outcomes. For the rhDNase users the results were as follows: 91.77 ml (95% CI 30.85 to 152.69) for change in FEV_1, 4.57 (95% CI 1.33 to 7.80) for % change in FEV_1, 2.73 (95% CI 0.94 to 4.52) for % predicted FEV_1 and 106.09 ml (95% CI 28.27 to 183.91) for FVC. For the group for whom rhDNase was unsuitable, the change in FEV_1 was 162.32 ml (95% CI 51.77 to 272.87).

4.29 The ERG's pooled analyses found that for the adult rhDNase users, there were no differences between mannitol and control in the incidence of PDPE (RR=1.00, 95% CI 0.61 to 1.66), and no significant difference in the rate of PDPE per year (RR=1.14, 95% CI 0.75 to 1.73). There was a significant change in FEV_1 compared with control, with a mean difference of 91.77 ml (95% CI 30.85 to 152.69). In the group for whom rhDNase was unsuitable, there were also no significant differences between mannitol and control in the incidence of PDPE (RR=0.44, 95% CI 0.18 to 1.10), but there was a significant change in FEV_1 with a mean difference of 162.32 ml (95% CI 51.77 to 272.87). The issues surrounding statistical power created by the change in the therapeutic indication to an adult-only population were compounded by the post-hoc subgroup analyses of the pooled trial data, and contributed to the uncertainty around the results.

4.30 The clinical effectiveness results were tabulated by the ERG according to rhDNase subgroup. They include separate findings for

the DPM-CF-301 and DPM-CF-302 trials and the pooled results (table 5).

Table 5 Clinical effectiveness results for rhDNase subgroups (taken from table 7 of the ERG report)

Outcome	Effect of mannitol in combination with rhDNase in adults	Effect of mannitol alone in adults who are ineligible, intolerant or inadequately responsive to rhDNase
Mortality	NR	NR
Exacerbations: - PDPE incidence	301: RR = 0.76 (0.43, 1.34)*** 302: RR = 1.92 (0.66, 5.56) Pooled: RR = 1.00 (0.61, 1.66)	301: RR = 0.54 (0.17, 1.70)*** 302: RR = 0.31 (0.07, 1.46) Pooled: RR = 0.44 (0.18, 1.10)
- PDPE rate per year	301: Rate ratio = 0.89 (0.57, 1.40)*** 302: Rate ratio = 4.37 (1.53, 12.48) Pooled: Rate ratio = 1.14 (0.75, 1.73)	301: Rate ratio = 0.64 (0.18, 2.27)*** 302: Rate ratio = 0.30 (0.05, 1.81) Pooled: Rate ratio = 0.50 (0.18, 1.40)
Lung function: - Change in FEV_1	301: MD = 109.27 (52.77, 165.77)** 302: MD = 88.45 (-8.46, 185.36) Pooled: MD = 103.99 (55.18, 152.80)	301: MD = 146.98 (*19.42, 274.54*)*** 302: MD = 208.60 (*-13.00, 430.20*) Pooled: MD = 162.32 (51.77, 272.87)
- % change in FEV_1	301: MD = 93.95 (*15.58, 172.32*)*** 302: MD = 88.45 (*-8.39, 185.29*) Pooled: MD = 91.77 (30.85, 152.69)	
- % predicted FEV_1	301: MD = 4.19 (0.31, 8.07)** 302: MD = 5.43 (-0.40, 11.31) Pooled: MD = 4.57 (1.33, 7.80)	
- FEV_1 response	301: MD = 2.66 (0.59, 4.73)** 302: MD = 2.95 (-0.61, 6.50) Pooled: MD = 2.73 (0.94, 4.52)	
- FVC	NR	
	301: MD=117.42 (1.00, 233.85)** 302: MD=96.94 (-7.68, 201.55)	

	Pooled: MD = 106.09 (28.27, 183.91)	
Respiratory symptoms	NR	NR
Exercise tolerance	NR	NR
Adverse events	NR	NR
Quality of life: - CFQ-R	NR	NR

4.31 The ERG conducted an indirect comparison of mannitol with hypertonic saline, in line with the scope. The only study found was Elkins et al. (2006), which included both children and adults, and did not stratify according to rhDNase use. The two measures common to both Elkins et al. and the studies used by the manufacturer were measurements of FEV_1 and pulmonary exacerbations. The ERG found that mannitol improved FEV_1 compared with hypertonic saline, although this was only statistically significant for the subgroup ineligible for rhDNase (94.32 ml, 95% CI 29.02 to 159.62), but not for the subgroup receiving rhDNase (23.77 ml, 95% CI -64.95 to 112.49). The ERG indicated that hypertonic saline seemed superior to mannitol in reducing pulmonary exacerbations, but the ERG did not attempt a comparison because the specific outcome measures for pulmonary exacerbations were very different. Overall the ERG stated that these results should be interpreted with caution because of the heterogeneity of the studies and the uncertainties of the data.

Clinical effectiveness evidence summary

4.32 The manufacturer's submission was based on two randomised controlled clinical trials, DPM-CF-301 and DPM-CF-302. The manufacturer's submission provided high-quality data, but the change in the therapeutic indication reduced the statistical power of the analysis. Mannitol was found to statistically significantly

improve the key outcome, FEV_1, but did not statistically significantly improve pulmonary exacerbations in either the rhDNase users or non-users. The ERG was concerned about lack of reporting of outcomes for the rhDNase subgroups and the merging of all those not receiving rhDNase into one non-rhDNase group. In the ERG's view data should have been presented for those who are ineligible, intolerant or who have an inadequate response to rhDNase.

5 Comments from other consultees

5.1 Professional groups pointed out that the position of mannitol within the clinical treatment pathway was not clearly defined. All consultees pointed to the Cystic Fibrosis Trust's standards for care as the standard of care for cystic fibrosis in the UK. Several professional groups also highlighted the advantages of a dry powder over nebulised solutions, and particularly mentioned the unpleasant aftertaste of hypertonic saline, which is administered as nebulised solution. There was little anticipated additional cost for training of either staff or patients in the use of mannitol.

5.2 There were no comments from patient groups.

5.3 The comments from NHS organisations were similar to those from the professional groups. They were also unsure of the position of mannitol within the treatment pathway, and one organisation suggested that rhDNase would be used as a first-line treatment, with mannitol reserved for second-line treatment, or as an add-on therapy. NHS organisations did not foresee any specific regional implications or significant additional clinical treatment if mannitol is adopted.

6 Cost-effectiveness evidence

6.1 In a systematic review of the literature the manufacturer did not identify any studies of the cost effectiveness of treating cystic fibrosis with mannitol. The manufacturer therefore developed a de novo economic model.

6.2 The manufacturer developed a Markov health-state transition model, taking into account individual patient pathways over a life time horizon. The timescale of the cycle lengths were taken from the DPM-CF-301 and DPM-CF-302 trials, and were 6 weeks for the first cycle, 8 weeks for the second cycle and 12 weeks for each subsequent cycle. Transition between the health states depended on clinically-derived features such as age, history of pulmonary exacerbations and use of mannitol. The analysis was conducted from an NHS and personal and social services perspective, and had a time horizon of 100 years, at which point all patients have died.

6.3 The health states assessed in the model are cystic fibrosis, cystic fibrosis with improved respiratory symptoms, lung transplant, death from cystic fibrosis, death from an unrelated cause. At baseline, all patients enter in the cystic fibrosis health state. As patients progress, if at any point their FEV_1 falls below 30%, they enter the lung transplant state in which they have a probability of receiving a transplant in subsequent cycles. Patients in the mannitol arm who do not respond to mannitol treatment in the first cycle (6 weeks) stop mannitol and switch to standard therapy (described previously as multiple medications and drug therapy, including inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for patients with diabetes). Modelled to mirror the clinical trial, the

definition of a response was either a relative increase of ≥ 5% or an absolute increase of ≥100 ml in FEV_1 at week 6 from baseline. In subsequent cycles, a patient may switch between 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_1% (including natural decline with age) were updated during each cycle of the model.

6.4 The clinical effectiveness data presented in the submission were not used directly; instead transition probabilities were derived from the clinical trials and from the literature, and incorporated into the model through regression analysis. The baseline characteristics such as age, gender, BMI and FEV_1% predicted were taken from the pooled adult population from the DPM-CF-301 and DPM-CF-302 trials. The natural decline in FEV_1% and the risk of an exacerbation were taken from the BioGrid retrospective observational study of the disease progression of cystic fibrosis (commissioned by the manufacturer). BioGrid Australia is a large scale online data collecting platform, designed to encourage data sharing between researchers in biomedicine. It has collated information from 12 sources ('data dictionaries') on cystic fibrosis, ranging from 1946 to the present. The probability of death was extrapolated from the BioGrid data using the life table method, with FEV_1% predicted as a covariate. Other risk factors for mortality were concurrent *Burkholderia cepacia* complex infection, which can lead to pneumonia in people with cystic fibrosis, transplantation mortality, and risks associated with age and gender. The transition probability parameters for mannitol response, FEV_1% predicted, effect of treatment on pulmonary exacerbations and improvement in respiratory symptoms were based on the data collected from the trials. FEV_1% predicted decline was modelled using age, age over

30, pulmonary exacerbations, FEV_1% predicted for patients aged under and over 30, and FEV_1% predicted for patients aged under and over 30 who did or did not have an exacerbation. Mortality was modelled using relative risk of death as a result of a *Burkholderia cepacia* complex infection in combination with an exacerbation, and the hazard rate for FEV_1% predicted. Other comorbidities and factors were not included as variables in the manufacturer's submission because the manufacturer did not expect mannitol to affect them. After a request for clarification from the ERG, these data were provided for the subgroups of rhDNase non-users (those ineligible, intolerant or who have an inadequate response to rhDNase).

6.5 Utility values were largely drawn from HUI data collected during the DPM-CF-302 trial and a literature search, along with information from the literature on utilities associated with lung transplant and pulmonary exacerbations. A HUI2 global utility score was determined for each patient according to the HUI Procedure Manual. There was no mapping of the HUI2 data to EQ-5D data. The baseline utility was taken as the mean overall HUI2 global utility score at screening before randomisation irrespective of treatment. The change in utility was calculated as the change between baseline and visit 3/week 14 or at the termination visit in the case of early withdrawal. The HUI2 global utility scores used in the cost-effectiveness analysis were obtained by adding the average change to the baseline utility for each health state. Utilities in the model for comparable health states (patients with improved respiratory symptoms and patients without improved respiratory symptoms) were treatment dependent. Utility data identified from the literature included the impact of pulmonary exacerbations on health-related quality of life and the impact of lung transplantation. The HUI questionnaire was administered in the study at weeks 0,

12, and 26 but has a recall period of 1 week, and so the data from DPM-CF-302 did not capture the effect of PDPEs on health-related quality of life for the trial population. Data on pulmonary exacerbations were taken from a poster presentation by Bradley et al. (2010) and from the Cystic Fibrosis Trust. After lung transplant patients were assumed to have the same utility values as those reported in Anyanwu et al. (2001). Adverse events had a negative impact on CFQ-R data collected from both trials. The base-case utility values used in the manufacturer's submission are presented in table 6.

Table 6 Base-case utility values presented in the manufacturer's submission (taken from table 74 in the manufacturer's submission)

Description of variable	Base-case value
Distribution baseline utility	0.899
Utility for patients treated with mannitol with improvement in respiratory symptoms	0.918
Utility for patients treated with best supportive care with improvement in respiratory symptoms	0.908
Utility for patients treated with mannitol with no improvement in respiratory symptoms	0.877
Utility for patients treated with best supportive care with no improvement in respiratory symptoms	0.853
Utility decrement for exacerbation	-0.23
Utility for patients with $FEV_1\% < 30$	0.31
Utility for patients with lung transplants	0.80

6.6 Costs for each health state in the Markov model were calculated for each treatment option at 26 weeks, but there was no distinction made according to respiratory improvement. Costs related to pulmonary exacerbation and lung transplantation were included, as were costs incurred after lung transplantation. Prices were taken from national reference costs. Costs were included for concomitant medications (mostly antibiotics) for both treatment options (control

and mannitol); the mean cost of concomitant medications was £2972 in controls and £3253 in patients receiving mannitol. Nearly all patients had at least one hospital visit, 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 trial period was £4391, with a PDPE this figure was £12,852. For patients in the control arm, the mean total costs without and with a PDPE were £4664 and £10,354 respectively (see table 7). Peri-transplant data were taken from UK literature. Resource use was taken from the trial and patient dossiers. A standard discount rate of 3.5% was applied.

Table 7 Costs for 26 weeks (6 months) of treatment for cystic fibrosis (taken from revised table 36 in ERG report)

	Cost (£)	Mannitol			Control		
			Mean	SD		Mean	SD
No PDPE in trial period	Medication		2871	4390		2617	2713
	Community visits		48	92		53	122
	Hospitalisations		1471	4323		1994	4474
	Total		4391	7136		4664	5492
PDPE in trial period	Medication		4797	3919		3976	4047
	Community visits		62	93		53	99
	Hospitalisations		7994	6829		6325	7561
	Total		12,852	7959		10,354	10,445
All patients	Medication		3253	4360		2972	3157
	Community visits		51	92		53	116
	Hospitalisations		2763	5551		3125	5745
	Total		6067	8032		6150	7510

6.7 Following clarification, the manufacturer's base-case results indicated an ICER for mannitol compared with control (best supportive care) of £41,074 per QALY gained for adults ineligible, intolerant or inadequately responsive to rhDNase and £47,095 per QALY gained for the adult rhDNase users (table 8).

Table 8 Results of the base-case analysis presented in manufacturer's submission (taken from table 1 in manufacturer's submission)

	Costs (£)	Incremental costs (£)	QALYs	Incremental QALYs	ICER (£)
Control	180,188		9.75		
Mannitol	211,923	31,735	10.52	0.77	41,074
Control with rhDNase	249,472		9.75		
Mannitol with rhDNase	285,858	36,386	10.52	0.77	47,095

6.8 The manufacturer undertook extensive deterministic sensitivity and scenario analyses. However, these analyses used the trial data for all patients rather than considering the two populations separately as in the originally proposed therapeutic indication. Many of the input parameters had little effect on the ICERs. Table 9 summarises those sensitivity analyses that changed the ICER by more than 10%, including probabilistic sensitivity analyses undertaken for the rhDNase non-user group.

Table 9 Sensitivity analyses that changed the ICER by ≥ 10%

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	0.00	0.00	31,735	0.77	41,074	31,735	0.77	41,074
Baseline patient characteristics								
FEV_1 % predicted CF patient at baseline	90.00	40.00	41,806	0.82	51,133	22,482	0.76	29,600
Estimated FEV_1 at week 26								
Regression parameter estimate for yes/no mannitol treatment used to predict the FEV_1 % predicted after 26 weeks of treatment	-0.09	3.14	25,506	0.42	60,703	36,148	1.01	35,775
Exacerbation								
Relative risk exacerbation with mannitol treatment - treatment responders	1.08	0.39	42,971	0.50	85,886	24,062	0.96	25,169
Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.00	1.82	34,311	0.71	48,109	30,882	0.79	39,091
Lung transplant and mortality								
Hazard rate FEV_1 % predicted	0.97	0.94	28,178	0.60	46,676	34,248	0.89	38,655
Utility								
Utility decrement for exacerbation	0.00	-0.33	31,735	0.76	41,734	31,735	1.23	25,727
Utility no improvement in respiratory symptoms mannitol arm	0.85	0.90	31,735	0.68	46,554	31,735	0.86	36,925
Utility no improvement in respiratory symptoms Control arm	0.90	0.81	31,735	0.63	50,743	31,735	0.93	34,245
Costs								
Cost of an exacerbation	376	9,012	40,063	0.77	51,854	27,529	0.77	35,631

6.9 The manufacturer also performed sensitivity analyses showing the effect of treatment failure after 1, 5, 10 and 20 years. Not maintaining the FEV_1 improvements over the long term had a large effect on the cost-effectiveness calculations. If the improvement in FEV_1 lasted 1 year the ICER was £149,587 per QALY gained, if the improvement lasted 5 years the ICER was £86,981 per QALY gained, if the improvement lasted 10 years the ICER was £63,539 per QALY gained, and if the improvement lasted 20 years the ICER was £49,907 per QALY gained.

6.10 The manufacturer conducted a number of scenario analyses. Those which had an impact on the ICER were the rate ratio of pulmonary exacerbations and the discontinuation rule, including the risk of previous PDPEs, costs and utilities (see below). However, incremental analyses included control and the aggregated rhDNase non-user group rather than separate analyses for each population in the proposed therapeutic indication compared with the appropriate comparator. The manufacturer concluded that the key drivers were:

- the cost of mannitol
- the relative risk of pulmonary exacerbations in the mannitol arm
- the impact of pulmonary exacerbations on a patient's quality of life
- the patient's FEV_1 % predicted when starting mannitol treatment
- the improvement in FEV_1 % predicted on mannitol treatment
- the hazard rate of FEV_1 % predicted
- utility for patients without improvement in respiratory symptoms.

6.11 Following clarification, the manufacturer submitted analyses on reduced adherence, which had the effect of reducing the costs in

the mannitol arms. Using a mean adherence rate of 85%, the sensitivity analysis conducted by the manufacturer gave an ICER of £33,934 per QALY gained for mannitol compared with control in rhDNase non-users, and £37,387 per QALY gained for mannitol compared with control in the rhDNase group. The manufacturer based these assumptions on the observed result that mean compliance was similar between mannitol responders and non-responders after week 6. At week 14 8% of the mannitol responders had withdrawn from treatment, and a further 7.6% had withdrawn by week 26.

6.12 There was uncertainty around the relative risk of pulmonary exacerbations, which meant that the model was sensitive to any fluctuation in this parameter, particularly regarding whether patients who did not respond continued with mannitol. Using relative risk of exacerbation for the total adult population, provided in the manufacturer's clarification letter, the ICER for mannitol compared with control was £27,673 per QALY gained in the rhDNase non-user group and £54,329 per QALY gained in the rhDNase user group. For the analysis requested during clarification using the relative risk of exacerbations for the rhDNase user and non-user group , the ICERs were £19,828 per QALY gained and £74,140 per QALY gained for the rhDNase non-users and users, respectively. The ICERs were particularly influenced by pulmonary exacerbations because they had an effect not only on healthcare costs, but also on quality of life (and therefore on the QALYs and ICERs).

6.13 The probabilistic sensitivity analyses conducted by the manufacturer was also queried by the ERG, because the analyses for the differences between the rhDNase group and the group ineligible for rhDNase used the pulmonary exacerbation rate in

patients with a mannitol response based on the overall pooled adult population.

6.14 In the manufacturer's probabilistic sensitivity analyses, mannitol alone had a 25.8% probability of being cost effective if the maximum acceptable ICER was £30,000 per QALY gained and a 10.9% probability if the maximum acceptable ICER was £20,000 per QALY gained. Mannitol as an add-on therapy had a 16.4% probability of being cost effective if the maximum acceptable ICER was £30,000 per QALY gained and a 7.4% probability if the maximum acceptable ICER was £20,000 per QALY gained.

6.15 After the manufacturer submitted further data in response to the ERG's request for clarification, the population was divided into an rhDNase group and a group ineligible for rhDNase (rather than the non-rhDNase group incorporating all those not taking rhDNase for reasons other than being ineligible, intolerant or having an inadequate response to rhDNase). This changed the values of several parameters used in the original probabilistic sensitivity analyses, and a new probabilistic sensitivity analyses was run. This resulted in mean ICERs of £53,796 per QALY gained for rhDNase group and £30,080 per QALY gained for the group ineligible for rhDNase.

6.16 The manufacturer conducted two subgroup analyses, by baseline FEV_1% predicted and by assuming that all patients receiving mannitol respond to treatment. The analyses show that as baseline FEV_1 % declines, the ICER decreases. For $FEV_1 \geq 80\%$, the ICERs are £50,688 and £56,228 per QALY gained for rhDNase non-users and users, respectively. For $FEV_1 < 40\%$, the ICERs are £23,704 and £30,746 per QALY gained for rhDNase non-users and users, respectively. When all those in the mannitol arm were assumed to

respond to mannitol treatment, the ICERs were £40,857 per QALY gained for rhDNase non-users, and £46,906 per QALY gained for rhDNase users.

Evidence Review Group comments

6.17 The ERG identified several issues with the cost-effectiveness evidence presented by the manufacturer. In the ERG's view the basic structure of this Markov model was appropriate for the research question. The structure of the model was deemed sufficiently inclusive and diverse to model the complexities of cystic fibrosis, but the ERG expressed some concerns about the cost-effectiveness results. There were a few mistakes in the model leading to odd results (such as QALY in the first year > 1), but these problems had a limited effect on the overall cost-effectiveness analysis. The ERG also highlighted some issues surrounding the parameter values. The ERG questioned the values used for the beta distribution for the utility decrement as a result of pulmonary exacerbation. The ERG also noted some concerns with the first- and second-order uncertainty values in the probabilistic sensitivity analyses, particularly for the distribution of the duration of an exacerbation and in the distributions used for the cost variables.

6.18 The ERG asked for a different population division according to rhDNase use than that provided in the manufacturer's original submission, but the new data provided by the manufacturer were not as complete as the ERG desired, with only lung function, change in FEV_1 and exacerbation reported for the relevant populations. The creation of two populations, adult rhDNase non-users and ineligible for rhDNase non-users, further reduced the statistical power of the manufacturer's data, which consequently increased the uncertainty of the cost-effectiveness results.

6.19 The ERG challenged the assumption made by the manufacturer that mannitol use was completely independent of rhDNase use, and that any benefit was in addition to rhDNase. This led to a reanalysis of the data based on different population divisions. Rather than grouping all patients not receiving rhDNase into one group, the ERG divided the group into those who were eligible to take rhDNase, and those who were ineligible to take rhDNase (in line with the proposed licence).

6.20 The ERG examined the manufacturer's validation of the model, and noted that the clinical results were not directly translated into the model, instead the manufacturer used regression equations. 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, and that each input and calculation had been checked by at least two statisticians and/or health economists. However, the ERG highlighted that there were inconsistencies within the model despite double checking. The manufacturer carried out extreme tests to check the plausibility of the model outcomes. 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 concluded that model validation was limited, but noted that the results of the validation checks carried out were similar to the results of the clinical studies at a time horizon of 26 weeks.

6.21 The ERG noted that one of the most important assumptions made by the manufacturer was that any improvement in FEV_1 would be maintained throughout the lifetime of the patient, and that it would be directly translated into lowered morbidity and mortality rates. This was taken from the BioGrid study, but there was also some evidence for a prolonged effect from the open-label phases of the

DPM-CF-301 and DPM-CF-302 trials. The BioGrid study was also used to provide hospitalisation costs, which may not be generalisable from the Australian setting to the UK. The ERG agreed with the manufacturer's assumption that patients whose condition did not respond to mannitol discontinue treatment.

6.22 The ERG was concerned about the several assumptions made by the manufacturer about pulmonary exacerbations, namely the narrow interval around the baseline rate used in the deterministic sensitivity analysis, based on the BioGrid data, and questioned its applicability to a UK population. The baseline rate for pulmonary exacerbations was set at 0.7 according to the BioGrid data, but Jarad et al. (2008) suggest this may be too low for the UK population. Also, the data collected did not include time to first exacerbation, which meant that the ERG could not calculate the rate of first exacerbation by patient years. The manufacturer's scenario analysis that increased the baseline exacerbation rate in the model to 1.5 decreased the ICER from £41,022 to £33,489 per QALY gained in the rhDNase non-user group, and from £47,085 to £39,629 per QALY gained in the rhDNase user group. This suggests that more pulmonary exacerbations would be prevented by mannitol, but the ERG stated that setting the rate at 1 returned the ICERs to approximately the original values.

6.23 The ERG was concerned about an assumption made by the manufacturer that HUI2 utility and cost parameters depended on treatment, and not on health state.

6.24 The ERG identified an unlikely outcome in the results for cystic fibrosis mortality. When assuming a 20% increase in cystic fibrosis mortality, the ICER increased from baseline, but when assuming a 50% increase in cystic fibrosis mortality, the ICER dropped below

that found for a 20% increase. There were a few differences in parameter values between the manufacturer's submission and the model, and some apparent errors. These were for the utility decrement resulting from exacerbation, distribution of the duration of an exacerbation, and in the distributions used for the various cost variables.

Exploratory analyses conducted by the ERG

6.25 The ERG conducted exploratory analyses to examine the effect on the ICER of varying the model assumptions and the input parameters used by the manufacturer. The parameters explored included the difference in costs and utilities of varying responses in terms of respiratory symptoms and exacerbations, and the hazard rate of cystic fibrosis mortality by FEV_1% predicted.

6.26 The ERG defined a new base-case analysis, which include the following amendments:

- The cost effectiveness of mannitol was analysed separately for two populations: rhDNase users and patients ineligible for rhDNase.
- The comparison for the rhDNase group was mannitol plus rhDNase against. rhDNase plus best supportive care.
- The comparison for the patients ineligible for rhDNase was mannitol monotherapy against best supportive care.
- Treatment-independent and improvement-specific values for costs and utilities were used to value health states.
- Relative risks for exacerbations were population specific.
- Costs of rhDNase were changed from £16.88 to the most recent price of £16.55 ('British national formulary' [BNF] 61).
- Adjustment to model parameters, probabilities and distributions.

6.27 The ERG's cost-effectiveness analysis included the treatment options of best supportive care, rhDNase and mannitol. As in the manufacturer's submission, there was an initial period of 6 weeks during which responsiveness to mannitol was assessed by FEV_1 measurements, and those whose condition did not respond were discontinued from treatment. In rhDNase users the ERG compared mannitol plus best supportive care and rhDNase with best supportive care and rhDNase. In patients ineligible, intolerant or inadequately responsive to rhDNase for rhDNase the ERG compared mannitol plus best supportive care with best supportive care. These amendments resulted in a new base case with ICERs for mannitol plus best supportive care compared with best supportive care of £29,883 per QALY gained for adults ineligible, intolerant or inadequately responsive to rhDNase and £80,098 per QALY gained for the adult rhDNase group (table 10). The main reason for the changes to the ICERs was the change from treatment-specific costs and utilities to health state-specific costs and utilities.

Table 10 The ERG's base-case analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) versus baseline (QALYs)
rhDNase users							
Control + rhDNase	265,610	11.27	9.79				
Mannitol + rhDNase	312,572	11.92	10.38	46,962	0.65	0.59	80,098
Ineligible for rhDNase							
Control	163,748	11.00	9.53				
Mannitol	210,683	12.65	11.10	46,935	1.65	1.57	29,883
ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years							

6.28 The ERG stated that despite its efforts to carry out an indirect comparison the data were not sufficiently robust to be included in a cost-effectiveness analysis.

6.29 In updating the manufacturer's model for the exploratory analyses the ERG used the same information from the BioGrid database for baseline cystic fibrosis data as the manufacturer to develop the parameter estimates (for example, the repeated measures mixed model estimate for FEV_1 decline over time). In addition, the ERG tested the relationship between FEV_1% improvement and survival, and found there was evidence to support the assumption that 1% improvement in FEV_1 was related to approximately 5% reduction in mortality. However, the ERG was not able to test the assumption that the probability of moving between health states remained the same over the lifetime of the patient because of a lack of data.

6.30 The ERG examined the assumption that the FEV_1% improvement caused by mannitol would be maintained over the lifetime of the patient. Varying this assumption had a large effect on the cost-effectiveness estimate. The ERG reduced the time horizon of the model as a proxy for shorter duration of effectiveness. The ERG assumed that if mannitol was to lose effectiveness, the effects would revert to best supportive care, and that patients would discontinue ineffective treatment within a short time. The ERG stated that this would mean that if mannitol and best supportive care were to become equal, the costs and effects for both arms would cancel the other out. The ERG re-ran the sensitivity analysis on the time horizon with their own assumptions, and this resulted in ICERs per QALY gained for a time horizon of 5 years of £188,551 for rhDNase users, and £90,126 for patients ineligible for rhDNase. For a time horizon of 10 years, the ICERs per QALY gained were

£127,625 and £49,854 per QALY gained for rhDNase users and patients ineligible for rhDNase respectively.

6.31 The ERG pointed out that the cost data were for patients receiving mannitol and the control group, rather than cost data by health state. The costs provided by the manufacturer were divided according to respiratory symptoms or according to rhDNase use, but not stratified by both. The ERG used the information available to calculate the ratio of the improvement-specific costs to the overall mean costs. The ERG calculated that patients with improved respiratory symptoms have 93% of the overall costs, whereas those without improved symptoms have 105% of the overall costs. The ERG assumed these percentages also applied to rhDNase mean costs. The ERG did not provide separate ICERs for these figures.

6.32 The ERG re-ran the probabilistic sensitivity analyses with assumptions based on its exploratory analyses and calculated that there was a zero probability that the ICER for mannitol would be below a threshold of £30,000 per QALY gained for rhDNase users. For patients for whom rhDNase was unsuitable, the probability that the ICER would be below a threshold of £20,000 per QALY gained was 5%, and the probability it would be below £30,000 was 50%.

6.33 Health-related quality of life data were the HUI2 data collected in the DPM-CF-302 trial. The ERG questioned the use of treatment-dependent utility and cost values, and the manufacturer acknowledged this to be a major assumption. The manufacturer provided separated sensitivity analyses based on rhDNase use/non-use, but there were insufficient data to investigate the effect of lung function. The ERG used the values derived from the manufacturer's clarification letter for utilities assuming utilities were

treatment independent. The manufacturer and the ERG did not identify any other substantial health-related benefits not included in the QALY calculation, apart from the possible reduction in burden of treatment related to a dry powder rather than a nebulised solution and referred to by the professional groups.

6.34 The effect of major changes in clinical or cost parameter, or structural changes on the size of the base-case ICERs are shown below in table 11.

Table 11 Changes in base-case ICERs when altering clinical or cost parameters (taken from table 58 in the ERG report)

Technologies	ICER (£)
Base-case manufacturer's submission, analyses based on total adult population	
Mannitol versus control	41,074
Mannitol + rhDNase versus control + rhDNase	47,095
Alternative manufacturer analyses based on subgroup analysis of clinical data	
Relative risk of exacerbation based on total adult population	
Mannitol versus control	27,673
Mannitol + rhDNase versus control + rhDNase	54,329
Relative risk of exacerbation based on adult rhDNase users	
Mannitol versus control	19,828
Mannitol + rhDNase versus control + rhDNase	74,140
Alternative ERG base case Relative risk of exacerbation population specific costs and utilities improvement specific instead of treatment specific	
Mannitol versus control	29,883
Mannitol + rhDNase versus control + rhDNase	82,508
Alternative ERG as above, time horizon 5 years	
Mannitol versus control	90,126
Mannitol + rhDNase versus control + rhDNase	188,551
Alternative ERG base case as above, time horizon 10 years	
Mannitol versus control	49,854
Mannitol + rhDNase versus control + rhDNase	127,625

6.35 The factors identified by the ERG as causing significant differences in the ICER estimates were:

- the stratification of rhDNase use into the adult rhDNase group and in the group ineligible, intolerant or inadequately responsive to rhDNase

- the assumption that any improvement in FEV_1 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
- the effect of pulmonary exacerbations on utility, and therefore on ICERs
- the uncertainty engendered by the lack of hypertonic saline as a comparator.

7 Equalities issues

7.1 The only equality issue raised was whether people with physical disabilities would be able to use the inhaler.

8 Innovation

8.1 There was no submission on the innovative quality of mannitol from the manufacturer, the ERG or the professional groups.

9 Authors

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Appendix A: Supporting evidence

There is no related NICE guidance for this technology.

Appendix B: Clinical efficacy section of the draft European public assessment report [if not yet published]

[To be added as a confidential appendix.]