NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Pharmaxis	**EXECUTIVE SUMMARY** We thank the Committee for an opportunity to comment on the preliminary Appraisal Consultation Document (ACD) of inhaled mannitol (Bronchitol®) in adult patients with cystic fibrosis (CF) [ID85]. In providing the following response, the manufacturer has sought to address as many of the Committee's and Evidence Review Groups (ERG) concerns as possible. A number of the concerns highlighted in the ACD have arisen as a result of the extended regulatory process to which Bronchitol has been subjected. Since the original submission to NICE (February 2011) the licensed indication has changed, as has the patient group for which the product is indicated in. In turn, this has had a substantial impact to the data and proposition with regards to the intended population. The manufacturer has taken on board the comments from committee and the ERG, and has also sought further guidance and clarification from the CF community. As a result, the manufacturer has undertaken a full review of the cost-utility analysis (CUA) presented to NICE. In providing this response, additional information and data analysis has been identified to improve the evidence-base and assist with highlighted areas of uncertainty. The proposal within acknowledges the comments received from the Committee and now more accurately reflects the needs of the CF community. We believe that this revised proposal would enable NICE to recommend access to a new treatment option in England and Wales for those CF patients that have the most unmet medical need and where Bronchitol delivers a significant step change in both efficacy and ease of use. **Revised proposition, cost-utility analysis and budget impact of Bronchitol to England and Wales**	The Committee considered the issues raised in the documents submitted by the manufacturer in response to the ACD. The Committee noted that several issues with the economic model had been addressed, but that substantial uncertainty remained. The Committee noted that the new stopping rule was likely to be implementable in clinical practice. The Committee was not persuaded that the BioGrid data set accurately reflected the UK population with CF. The Committee considered mannitol use in the context of the current treatment pathway and the survey commissioned by the manufacturer. The Committee concluded that the ICERs for all subgroups presented by the manufacturer (some based on the anticipated, but later amended wording of the marketing authorisation, for example people using rhDNase or people who cannot use rhDNase) were too high for mannitol to be an appropriate use of NHS resources. (see FAD section 4.25) The Committee was aware that mannitol improved lung function less in the people not using rhDNase than in people who cannot use rhDNase, and therefore found the ICERs in people not using rhDNase 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.(see FAD Section 4.26) The Committee agreed that people who cannot use rhDNase because of ineligibility, intolerance or
	To reflect the comments received by NICE and the needs of the CF community, the manufacturer has identified two CF patient populations who have the most unmet medical need and in which inhaled mannitol provides a significant clinical benefit. • **Patients receiving Best Supportive Care (BSC) without add-on rhDNase.** • **Patients receiving BSC (+/- rhDNase) experiencing a greater than 2% decline in FEV1 percent predicted per year.** In addition the manufacturer has consulted with CF clinicians about concerns raised by NICE that the stopping rule proposed was unlikely to be adhered to. As a result a 0% improvement in FEV1% predicted at 6 weeks is now proposed as a stopping rule in order to ease clinical implementation.	
	To assess the clinical and economic impact of these propositions, the CUA has been revised as follows: • To reflect the two base cases from the revised proposition (above) and the change in the	

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	stopping rule. • The CUA model was updated in line with comments received from the ERG and NICE. (Details of the revision are provided below and within the analysis reports attached). • To address concerns raised by the ERG and NICE, additional sensitivity and scenarios analysis have been modelled to examine: o the impact of key clinical and economic influences on the model, o the duration of treatment effect o drop-out rates Base case ICERs in the two sub-populations identified above were: • **£19,993 /QALY in patients receiving BSC without add-on rhDNase** • **£36,214/QALY in patients experiencing a greater than 2% decline in FEV1% predicted per year.** In probabilistic sensitivity analysis (PSA), for patients receiving BSC without add-on rhDNase, the probability of the ICER being below a willingness to pay (WTP) threshold of £30,000 was 82.2% and at a WTP of £20,000 was 46.5%. In patients experiencing a 2% decline in FEV% predicted per year, probabilities were 20.8% and 1.2%, respectively. The manufacturer noted NICE's concerns that Bronchitol might replace hypertonic saline (HS). The manufacturer commissioned independent market research that suggests that these concerns are unfounded (see patient pathway notes below). The manufacturer would still accept eligibility criteria in any NICE recommendation to prevent switching of patients from HS that may be otherwise well controlled should NICE deem this necessary. The manufacturer is reluctant to propose specific wording given that the use of HS at doses proven to be effective in reducing exacerbations is low, there has been no regulatory review of safety and efficacy, and no RCTs performed in patient populations with the same demographic makeup as patients found in UK CF clinics. Finally, in considering the eligible patient population likely to receive mannitol (based on the patient treatment pathway analysis), the estimated acquisition cost for Bronchitol in year-1 would be estimated as ~ £1.2M rising to £3.3M in year-5. This represents low cost compared to other treatment in CF	inadequate response to rhDNase, and whose lung function declined rapidly (yearly FEV1% 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. (see FAD section 4.28)

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	Current treatments CF is an inherited, orphan designated condition affecting an estimated 8,000 patients (estimated 4,200 adults) in the UK with a severely limited life-expectancy[1], just over half of whom are adults (defined as 18years+). Characterised by a rapid and progressive decline in lung function (FEV1) and frequent respiratory infections (exacerbations) that often lead to hospitalisation, the clinical goal for patients with CF is to prevent further loss in lung function which has been shown to correlate with increased risks of exacerbation and mortality. Current treatment reflecting BSC in the UK is complex and is based upon the individual needs of the patient. Treatment represents a significant patient and carer burden, with daily respiratory physiotherapy, nutritional control, inhaled/oral antibiotics, bronchodilators and inhaled/oral corticosteroids. To facilitate mucocillary clearance, patients may also receive aerosolised rhDNase (Pulmozyme®), and whilst unlicensed, nebulised hypertonic saline may also be given. **Clinical study design and results** Consistent with Regulatory advice at the time, the two Bronchitol® registration trials DPM-CF-301 (n=295) and DPM-CF- 302 (n=305) were individually powered to show (and demonstrated) statistically significant improvements in lung function for all patients (children and adults), when added to BSC. In October 2011, the EMA provided an initial indication for inhaled mannitol as a treatment in adult-only patients. This led to a reduction in the planned statistical power of the trial data, although due to the studies being of similar design and study population, the EMA accepted pooled analysis of adult patients in their evaluations (n=341). At the same time the patient population was simplified from '*...as either an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase' to '...add on therapy to best standard of care'*. The subgroup that is intolerant to or inadequately responsive to rhDNase was small and not predefined in both studies and was the subject of NICE concerns in the preliminary ACD. It is no longer in line with the Bronchitol approved label and has therefore been removed from the base case proposition.	
	In pooled analysis, when compared to Best Supportive Care (BSC with or without rhDNase), adult patients treated with Inhaled mannitol demonstrated: • A statistically significant improvement in lung function of 99.5mL($p<0.001$) over 26 weeks whilst control patients receiving BSC experienced an average ~8mL decline in lung function over the same time period. • This significant improvement in lung function was observed in all patients when added to BSC, regardless of patients comparatively receiving BSC, with (94.1 mL, $p<0.008$) or without (110.3 mL $p<0.005$) rhDNase. • The improvement in lung function was sustained to at least 78 weeks in open-labelled	

[1] **Source:** Population and Median age of death in the UK = 29 years old (min: 0- max:61), UK CF Trust Registry Report, 2010.

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	extension studies. • Patients switched from control to inhaled mannitol at 26 weeks, also experienced a substantial improvement in lung function. After 52 weeks of treatment, these patients had regained similar levels of lung function to those that had received inhaled mannitol throughout the trial. • A lower exacerbation rate, with reductions in the incidence of protocol defined pulmonary exacerbations (PDPE) in the adult population of 24% (95% CI: 0.51; 1.13), when compared to BSC. Despite insufficiencies in sample sizes and event rate frequencies to satisfy statistical rigour, this consistency in trend was observed in all sub-groups • A significant difference in PDPE rates was observed when compared to patients receiving BSC without rhDNase (Rate Reduction: mannitol: 0.38 vs. control: 0.97) • A significant improvement in lung function and reduction in exacerbations in patients receiving BSC (+/-rhDNase) but experience the most rapid deterioration in lung function (> 2% annual decline in FEV1% predicted per year). Based on pooled data used in the CUA, change from baseline in FEV1% predicted at 26 weeks was -1.10 (95%CI: -3.72-1.52) in patients treated with BSC (+/-rhDNase) and in patients treated with inhaled mannitol: 2.71 (95% CI: 0.54-4.87), with relative exacerbation rates of 1.37 and 1.14 per year, respectively. • An early response to treatment. After 6 weeks of treatment, an improvement in lung function was highly predicative of a continued response at 26 weeks. • The overall safety profile of inhaled mannitol was favourable, with the most common side effects being manageable. **Bronchitol has the potential to delay the progression in lung function decline for patient with CF, and in turn reduce the associated risks of exacerbation and mortality. Bronchitol brings a clear step change in efficacy and ease of use to a patient population that has a median age of death of 29 years.**	
	Manufacturer's responses to the preliminary ACD For ease of review, in addressing areas of uncertainty highlighted by the Committee in the ACD, the manufacturer has grouped the responses by theme. In addition, the manufacturer has identified additional information and analysis to improve the evidence-base. These data have been described below: **Points of factual error:** A number of factual and accuracy errors were identified in the ACD. These have been highlighted with proposed corrections stated. **Trial design, choice of primary end point and FEV_1:** Provides further clarification of the trial design (with protocols attached); reasons for the choice of primary endpoint (FEV_1 percent predicted) and further details of its calculation as change over time. **Points of important clinical note:** The manufacturer strongly disagrees with the comments in the ACD that Bronchitol does not represent a step change in treatment. This response	

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	highlights the medical advancement and innovation value consistent with Sir Ian Kennedys report on promoting innovation within the UK[2], that inhaled mannitol brings to patients with CF, and is further supported by a consensus statement of over 60 European CF physicians, including 12 physicians from the UK (attached). **Points of clarification on the model design:** Clarification and corrections in the accuracy of the data in the manufacturers CUA, as highlighted in the preliminary ACD. In acknowledging the ERG comments on the model, a revised base case has been produced to reflect the framework and parameter modifications proposed by the ERG, with additional data derived from the actual patient-level data from the trials to improve accuracy. Full details are provided below and within the analysis report and models attached **Method and choice in extrapolating long-term outcomes:** In order to extrapolate a life-time experience for patients with CF (beyond that captured within the trial period), a longitudinal, patient-level dataset was required for the CUA. In the original MS a non-UK dataset (BioGrid) was used. The use of this data was heavily criticised in the draft ACD. This section provides the rationale for using this data as the only source of longitudinal patient-level data available at the time, and provides additional research commissioned from the independently owned BioGrid dataset, to further support the UK comparability and appropriateness of using the data. **Proposed patient inclusion criteria:** Two CF patient populations are proposed. 1. **Adult CF patients not currently taking rhDNase** The simplification of the final EMA approved label to "...as an add on therapy to best standard of care" occurred after the manufacturer's NICE submission and reflected advice given to the CHMP by its Scientific Advisory Group that the original label referencing a subgroup that were "..intolerant to or inadequately responsive to rhDNase" was clinically inappropriate. The manufacturer now proposes for the first time a subgroup which was clearly defined in the study; those CF patients currently not taking rhDNase. This was a significant subgroup (Bronchitol: n=85; Control: n=49) and given that the majority of adult patients in the UK today have already trialled rhDNase those patients who are not now taking rhDNase by definition have a high unmet medical need. In the pooled trial data the patients not taking concurrent rhDNase had a greater treatment effect in both lung function (110.3 mL p<0.005) and reduction in exacerbations (Rate Reduction: mannitol:0.38 vs. control:0.97) than the ITT population. 2. **Adult CF patients with a historical lung function decline of greater than 2% per annum** In further evaluating sub-populations of patients by their annual rate of decline in lung	

[2] www.nice.org.uk/aboutnice/howwework/researchanddevelopment/KennedyStudyNICEResponse.jsp

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	function, both within the BioGrid dataset and from the two registration trials (DPM-CF-301 and DPM-CF-302), it is clear that patients presenting with the most rapid deterioration in lung function experience the most exacerbations and have the lowest life-expectancy. This is supported by a number of published studies (Liou *et al.,* 2010; Schluchter *et al.,* 2006; and Taylor-Robinson *et al.,* 2012), and represents a significant unmet need within current CF treatment. In further analysis of the pooled trial data, inhaled mannitol demonstrates a greater treatment effect in these patients; significantly reducing lung function decline and exacerbations experienced. The proposition of inhaled mannitol for patients that experience a greater than 2% decline in lung function per year is supported by the treatment effect seen in trial data and addresses a significant unmet need for CF patien*ts.* Furthermore, from consulting with the CF community the manufacturer understands that similar rules are being recommended to assist as evaluation criteria for more expensive treatments for CF patients in UK clinical practice. **Proposed stopping rules:** The manufacturer recognises that previously introduced stopping rules for rhDNase (based on an improved lung function response) have been difficult to clinically administer in UK CF centres because of a lack of proven correlation between FEV_1 response and a reduction in exacerbations. Whilst a stopping rule for rhDNase is not supported by the clinical data the converse is true for inhaled mannitol. Data from the inhaled mannitol trials clearly shows that a FEV_1 response at 6 weeks is a very sensitive and specific predictor of the response at 26 weeks. In addition, patients demonstrating any improvement in FEV_1 over the 26 weeks of the study had 59% fewer exacerbations than those that experienced a decline in lung function. A stopping rule based on FEV_1 improvement at 6 weeks is therefore clinically and scientifically validated, appropriate to improve the cost-effectiveness of a treatment, and relevant for patients encumbered with a heavy treatment burden. In recognising the Committee's concerns of implementing a stopping rule requiring a patient to achieve a 100mL or 5% improvement in FEV1 (absolute or % predicted), the manufacturer proposes to modify the continuation criteria at 6 weeks to a >0% improvement. In doing so, the sensitivity and specificity in predicting response at 26 week is retained. The cost-effectiveness is decreased slightly, but this trade-off is accepted given feedback from senior CF clinicians that a 0% cut off will improve patient acceptance and clinical implementation of the stopping rule. **Patient treatment pathways:** As highlighted by the Committee, the treatment of CF is complex. Treatment is tailored to the patient's needs and clinical guidelines reflect an individualised approach to protocols. Prescribed treatments for CF are not captured or available in the UK public record in sufficient detail to be able to derive insight upon which to evaluate a patient treatment pathway. To be able to evaluate the unmet needs of current treatments for adults with CF an independently commissioned survey examined rhDNase and hypertonic saline usage; treatment satisfaction; and how physicians would use inhaled mannitol. The survey captured data from 29 CF respiratory physicians from at least 10 of the	

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	19 adults centres within the England and Wales. The points most relevant for this evaluation are summarised below and full details are provided in the attached report. Of particular note: • Only 18% of adult patients (aged 18 and over) have never used rhDNase or hypertonic saline and consequently the opportunity for inhaled mannitol to be used as a first line agent is very small. • About one third of patients are perceived by clinicians to be uncontrolled irrespective of the treatment they are taking. This underlines the level of unmet need which exists in the adult CF population despite the widespread use of existing treatments • Clinicians see inhaled mannitol as a potentially useful treatment particularly in patients who are not well controlled despite treatment with hypertonic saline and/or rhDNase (50% of the proposed population), and a beneficial option for patients not currently receiving treatment (19%). • Inhaled mannitol was not perceived as a treatment that will replace existing treatments on a significant scale when those patients are well controlled. • The % of patients on hypertonic saline who are well controlled that would be considered for a trial on inhaled mannitol is very low (11%). Extrapolating these results to the CF population in the UK the proposed potential Bronchitol-treated population would be 1,000 patients. This compares with the 4,000 patients currently estimated to be on rhDNase and the 3,600 patients estimated to be on hypertonic saline**.**	
Sandwell PCT	**RE: Mannitol dry powder for inhalation for the treatment of cystic fibrosis** On behalf of Sandwell PCT, we would like to submit our response on the appraisal consultation document for mannitol dry powder for inhalation for the treatment of cystic fibrosis. We are in agreement with the ACD recommendation for NHS authorities not to fund mannitol for this indication as on the basis of the evidence submitted, it is unlikely that this treatment will be clinically and cost effective in every day clinical practice. More specifically: **1) Mannitol dry powder for inhalation for the treatment of cystic fibrosis is not a cost-effective use of NHS resources.** The Evidence Review Group's (ERG) analyses led to ICERs above £30,000 per QALY gained. These calculations were associated with considerable uncertainty, however the appraisal committee judged that the ICERs were unlikely to fall	The Committee concluded that the ICERs for all subgroups presented by the manufacturer (some based on the anticipated, but later amended wording of the marketing authorisation, for example people using rhDNase or people who cannot use rhDNase) were too high for mannitol to be an appropriate use of NHS resources. (see FAD section 4.25) However, 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 FEV1% 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.

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	below £30,000 per QALY gained even when this uncertainty was taken into account. **2)** As we had the opportunity to ascertain during the appraisal committee, **the position of mannitol in the treatment pathway for cystic fibrosis is unclear.** It is likely for many patients will be an add-on therapy to standard care. **3) There is uncertainty around modeling the cost effectiveness of mannitol**. In the economic model submitted by the manufacturer, the measurement of lung function used was FEV_1 predicted rather than the primary outcome of the trials, absolute FEV_1. Additional concerns or inconsistencies included: • the assumption used by the manufacturer in the cost-effectiveness model that improvements in lung-function would be maintained over the life of the patient, and that these would directly translate into lower morbidity and mortality; • the utility values for the same health state which varied according to treatment arm; and • the use of Australian rather than UK data on the natural history of the disease. • There was also uncertainty over adherence to treatment, and whether doctors and patients would adhere to the stopping criteria assumed in the model (as indicated by the medical expert during the 3rd April meeting). • It was also found that the impact of adverse effects had not been incorporated into the model sufficiently. **4) There are limitations to the research quality.** The manufacturer presented the pooled results from 341 adult participants from two RCTs. Participants were stratified into rhDNase users and non-users so consequently even the pooled analyses were often underpowered. In the ERG's view, rhDNase non-users should have been further divided into those ineligible, intolerant and those with an inadequate response to rhDNase. The	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. (see FAD section 4.28) The Committee was aware of the uncertainties in the modelling. See FAD Sections 4.14, 4.15, 4.16, 4.17) The Committee was concerned by the post-hoc stratification of the two key trials and other uncertainties in the clinical evidence (See FAD Sections 4.3, 4.5, 4.6, 4.8, 4.10), but concluded that there was sufficient evidence of the clinical effectiveness of mannitol to reach a decision (See

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	long-term effects of mannitol, and the effects of mannitol on mortality, are unknown. Hypertonic saline was not included as a comparator. **5) There were concerns over the design of the trials and the analyses.** The appraisal committee concluded that there were significant concerns about the design of the trials and the resulting analyses, as the manufacturer did not submit a trial protocol; the primary outcome changed from change in FEV_1 from baseline to week 26 to change from week 6 of treatment to week 26; unblinding was a concern of the committee; and baseline FEV_1 was included as a covariate. **6) We agree with the appraisal committee opinion that mannitol does not represent a step-change in treatment.** Therefore it does not meet one criterion for early access to the NHS of interventions that might be innovative. **7) Treatment with mannitol will cost about £43,000 per year per 100,000 population.** This is assuming that all patients with cystic fibrosis aged over 18 years of age are prescribed mannitol, in line with its proposed licence as an add-on therapy. It is not clear how many patients will benefit from treatment or how this will affect their lives. Finally: • The trials compared twice-daily 400mg mannitol versus mannitol at a sub-therapeutic dose of 50mg in addition to best supportive care with or without rhDNase in people without hyper-responsiveness to mannitol. Patients taking nebulised hypertonic saline were excluded. The trials had 26-week double-blind phases, followed by an unblinded phase of 26 to 52 weeks. The primary outcome of these trials was change in absolute forced expiratory volume in 1 second (FEV_1) from baseline to week 26. The manufacturer stated that this was changed to change in absolute FEV_1 from week 6 to week 26 at the appraisal committee meeting. The committee was concerned that the manufacturer did not submit the protocol for the trials. • There were differences in the population, comparators and outcomes listed in the scope and those addressed by the manufacturer's	FAD section 4.13). The Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29) It is not within the remit of NICE to consider the financial impact of recommendations on individual PCTs.

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	submission. The population specified in the final scope was people with cystic fibrosis. The manufacturer presented results from adults only - in line with the likely licence. The manufacturer compared mannitol versus best supportive care, rather than the other potential comparators specified in the scope (rhDNase or hypertonic saline). The manufacturer indicated that mannitol should be considered as an add-on therapy, as this is the current indication. Mortality, a listed outcome in the scope, was not assessed in the trials. • **Quality of life:** There were no statistically significant changes in quality of life in either trial with mannitol, as measured by the Cystic Fibrosis Questionnaire-Revised (both trials) and the Health Utility Index 2 (one trial). The appraisal committee noted that EQ-5D quality of life data was not submitted. The manufacturer did not submit any data on mortality, and did not submit data on individual components of the FEV_1 response, respiratory symptoms, adverse events or health-related quality of life for the two rhDNase subgroups.	

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British Thoracic Society	The conclusions of this NICE STA are disappointing. The decision that 'Mannitol is not recommended for the treatment of cystic fibrosis in adults as an add-on therapy to best standard of care' seems to be a rather strong statement when the committee concluded 'that mannitol has a positive clinical effect on lung function in the short term but there was uncertainty about the magnitude of the effect of mannitol….'. (Section 4.15). We note that NICE has reviewed the data in detail, and the analysis of the data seems accurate: The study by Bilton et al Eur Resp J 2011;38:1071-1080 showed favourable results for FEV1 and exacerbations; The study by Aitken at al (Am J Resp Crit Care med 2012;185:645-652) also suggested favourable effects, although it must be acknowledged that they did not reach statistical significance, and NICE has discussed this in detail. The British Thoracic Society's view is that these results should encourage use of mannitol in specialist CF centres with assessment of benefits in individual patients, rather than the decision that this is 'not recommended' which we would regard as too strong an interpretation of the clinical evidence discussed. We note that the cost-effectiveness analysis is, of course, highly complex and not entirely convincing.	The Committee concluded that mannitol is clinically effective in improving both lung function (FEV1) 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. (See FAD Section 4.13). 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 FEV1% 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. (see FAD section 4.28)
Cystic Fibrosis Trust	The Cystic Fibrosis Trust is the UK national charity for people living with Cystic Fibrosis. The Trust funds world-leading medical research, ensures safe and appropriate clinical care, and offers direct support for people with Cystic Fibrosis and their families. Cystic Fibrosis is an inherited and progressive life-limiting disease which affects internal organs (particularly the lungs and digestive system) by clogging them with thick sticky mucus. This makes it harder to breathe and to digest food. The mucus in the lungs provides an ideal environment for pathogenic bacteria, promoting recurrent and increasingly frequent respiratory infections. In 2009, the average age at death was only 27. **Response to the consultation** The Cystic Fibrosis Trust is very disappointed by NICE's initial decision not to recommend mannitol dry powder for inhalation for the treatment of cystic fibrosis.	

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	We firmly believe that not enough emphasis has been placed on how mannitol will help to relieve the burden of treatment and care for people with Cystic Fibrosis, and therefore this important evidence has not been taken into account when arriving at the initial decision. People with Cystic Fibrosis routinely have to undergo hours of treatment and physiotherapy every day. Maintaining this regime is time consuming, exhausting and impacts on quality of life. New treatments that help to alleviate this burden, encourage adherence and therefore improve clinical outcomes, have been slow to come through the therapeutic pipeline. Cystic Fibrosis clinicians need more treatment options to be made available for people with CF. mannitol would be available to a broad population of CF patients, irrespective of microbiological status. This is the first innovation to be approved to tackle the fundamental issue of airway clearance in 18 years. This treatment is a step change in terms of improving quality of life for people with CF, specifically because mannitol is a dry powder inhaled treatment that is very quick and easy to administer. The importance of this new application cannot be overstated in terms of convenience and ease of use. The drug delivery device can be carried in a small bag and administered at times convenient to the person with CF. The drug is also easy to take at the right dose and frequency, important factors in improving adherence, so that the full benefit of the treatment can be received. Currently, mannitol would offer the only alternative to nebulised hypertonic saline which is significantly more time consuming and less convenient when taking into account the need for preparation and repeated cleaning. Also, it is not well tolerated in all patients, increasing cough and wheeze significantly and has an unpleasant taste when inhaled via nebuliser. The CF Trust regularly hears from people with CF that these factors negatively impact on adherence and are likely, therefore, to lead to poorer clinical outcomes. This treatment is also a step change in terms of its effectiveness in CF. It has a clear clinical benefit as it limits lung damage by reducing exacerbations by 24 per cent. Exacerbations are now accepted as a major factor in long term FEV1 decline. The goal for most adult CF patients is to maintain FEV1 for as long as possible and any improvement in an already heavily treated	The Committee was aware of the difficulties patients with Cystic Fibrosis face 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. (see FAD Section 4.4) The Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29) The Committee concluded that mannitol is clinically effective in improving both lung function (FEV1) and pulmonary exacerbations in people with cystic fibrosis. The Committee further concluded that there are subgroups of people who may experience

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	patient group is dramatic. Therefore, FEV1 improvements of greater than 100ml are meaningful in CF. The importance of maintaining and improving FEV1 cannot be underestimated both in terms of improving health outcomes and improving quality of life. Poor lung function and frequent exacerbations increase the likelihood of needing intravenous antibiotics and time spent in hospital, which not only has a significant impact on people with CF, but also their family and carers. Reduced time spent in hospital also help people with CF stay away from the risks of cross infection, which is also key to improved long term outcomes and survival. It also means that they are able to continue to work and live their lives as normally as possible. The treatment burden in CF is such that any treatments that are not being adhered to or that are not having a clinical benefit will stop being prescribed. Treatments that don't produce a benefit would routinely be stopped by CF clinicians. As stated above, people with CF have a huge burden of treatment and physiotherapy to endure everyday. If they feel that a treatment is not working they will discuss this with their clinical team. The proposed introduction of mannitol represents a small budget impact in the context of other treatments currently available for CF and would benefit a broad population of CF patients. In fact, there could be potential cost savings to be made from reducing the need for hospitalisation due to repeat exacerbations. Therefore, the Cystic Fibrosis Trust is of the opinion that the provisional recommendations from NICE regarding mannitol are not a sound and a suitable basis for guidance to the NHS.	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. (See FAD Section 4.13). NICE cannot consider budget impact but must consider a technologies cost effectiveness. Cost savings from reduced need for hospitalisations are fully included in the economic modelling approach.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.
Royal College of Nursing	**Introduction** The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for on the use of Mannitol dry powder for inhalation for the treatment of cystic fibrosis. Nurses caring for people with cystic fibrosis reviewed the documents on behalf of the RCN.	

Consultee	Comment	Response
	Appraisal Consultation Document – RCN Response The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below: i) **Has the relevant evidence has been taken into account?** The evidence considered seems clear and comprehensive. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries seem very clear. However, we would agree completely with the Committee's note that the studies have not been done comparing Mannitol with hypertonic saline. In our view, this should have been the main comparator and it would have been very useful to have this data. We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with cystic fibrosis. The preliminary views on resource impact and implications should be in line with established standard clinical practice. iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology. Iv) **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** None that we are aware of at this stage.	Comment noted. 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. (See FAD Section 4.10) The Committee took into consideration the treatment pathway survey provided by the manufacturer in response to the ACD and 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. (See FAD section 4.3) Comment noted.

Consultee	Comment	Response
	v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	NICE routinely makes available equality impact assessment on all pieces of guidance published.
Royal College of Physicians	Please take this email as confirmation that the RCP wishes to endorse the response from the British Thoracic Society to the NICE STA: Cystic fibrosis - mannitol [ID85] - Appraisal Consultation Document (ACD).	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
CF consultant	Thank you for giving me the opportunity to comment on the NICE appraisal for mannitol. I was impressed by the level of interest and commitment from the NICE committee and in particular the very fair handling of the appraisal meeting. I have concerns about the current conclusions of the appraisal because the advice as it stands would prejudice against the group of CF patients who are experiencing a more rapid decline in lung function despite standard best therapies which would include a nebulised antibiotic , rHDNase and in some cases hypertonic saline. In that situation it would appear that a patient should receive a trial of mannitol. Two things have changed since the time of the mannitol appraisal which may allow the committee to review things further. A national commissioning policy has been developed for CF medicines which essentially has a stepwise approach for high cost drugs related to decline in lung function and /or increase in exacerbations. This document which has just been agreed by the Clinical Reference Group for CF Specialist commissioning may well help frame the use of Mannitol to	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. (see FAD section 4.27) 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 FEV1% 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. (see FAD section 4.28) The Committee cannot consider information outside

Nominating organisation	Comment	Response
	avoid what the NICE committee do not feel would be cost effective ie all patients with CF receiving this medication. I would suggest that as there is evidence of efficacy from the studies in patients who are already on best standard care that this new medication is targeted at patients who are failing on that best care. ie that a framework delineating a more rapid decline ie greater than 2 or 3 % per year or with more than 2 exacerbations requiring IV therapy are considered for a trial of therapy. CF adults do not wish to take medicines that do not result in improvement and I believe that a 6 week trial would give an indication of patients with a response. Subsequent to the NICE meeting we have presented data at the ECFS and have an abstract accepted for the NACF (the US scientific meeting) demonstrating that a response at 6 weeks is highly predictive of longer term response and so allows a stopping rule. As there is a close association between the lung function response and the exacerbation response I believe that a trial of therapy for a patient who is declining is a legitimate way to assess the medicine and prevents unnecessary long term use. Both these developments are post the appraisal committee meeting and I wished to ensure that they are considered. The national commissioning policy for CF drugs is just being ratified by the commissioners so that I am not at liberty today to send a copy through , however it will be available nationally within the next two weeks and I would urge the committee to review their decision and suggest that mannitol can fit as a key therapy for the patients unresponsive or intolerant of previous airway therapies.	an appraisal's remit or any potential future arrangements via specialist commissioning.

Comments received from commentators

Commentator	Comment	Response
CSAS	On behalf of the Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for mannitol dry powder for inhalation for the treatment of cystic fibrosis. We are in agreement with the recommendations in the ACD	

Commentator	Comment	Response
	not to recommend mannitol for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice. • **Mannitol dry powder for inhalation for the treatment of cystic fibrosis is not a cost-effective use of NHS resources.** The Evidence Review Group's (ERG) analyses led to ICERs above £30,000 per QALY gained. These calculations were associated with considerable uncertainty, however the Appraisal Committee judged that the ICERs were unlikely to fall below £30,000 per QALY gained even when this uncertainty was taken into account. • **The position of mannitol in the treatment pathway for cystic fibrosis is unclear.** It is likely it would be an add-on therapy to standard care. • **There is uncertainty around modeling the cost effectiveness of mannitol**. In the economic model submitted by the manufacturer, the measurement of lung function used was FEV_1 predicted rather than the primary outcome of the trials, absolute FEV_1. Additional concerns or inconsistencies included: the assumption used by the manufacturer in the cost-effectiveness model that improvements in lung-function would be maintained over the life of the patient, and that these would directly translate into lower morbidity and mortality; the utility values for the same health state which varied according to treatment arm; and the use of Australian rather than UK data on the natural history of the disease. There was also uncertainty over adherence to treatment, and whether doctors and patients would adhere to the stopping criteria assumed in the model. It was also found that the impact of adverse effects had not been incorporated into the model sufficiently. • **There are limitations to the quality of the research.** The manufacturer presented the pooled results from 341 adult participants from two RCTs. Participants were stratified into rhDNase users and non-users so consequently even the pooled analyses were often underpowered. In the ERG's view, rhDNase non-users should have been further divided into	The Committee concluded that the ICERs for all subgroups presented by the manufacturer (some based on the anticipated, but later amended wording of the marketing authorisation, for example people using rhDNase or people who cannot use rhDNase) were too high for mannitol to be an appropriate use of NHS resources. (see FAD section 4.25) However, 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 FEV1% 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. (see FAD section 4.28) The Committee was aware of the uncertainties in the modelling. See FAD Sections 4.14, 4.15, 4.16, 4.17) The Committee was concerned by the post-hoc stratification of the two key trials and other uncertainties in the clinical evidence (See FAD Sections 4.3, 4.5, 4.6, 4.8, 4.10), but concluded that there was sufficient evidence of the clinical effectiveness of mannitol to reach a decision (See FAD section 4.13).

Commentator	Comment	Response
	those ineligible, intolerant and those with an inadequate response to rhDNase. The long-term effects of mannitol, and the effects of mannitol on mortality, are unknown. Hypertonic saline was not included as a comparator. • **There were concerns over the design of the trials and the analyses.** The Appraisal Committee concluded that there were significant concerns about the design of the trials and the resulting analyses, as the manufacturer did not submit a trial protocol; the primary outcome changed from change in FEV_1 from baseline to week 26 to change from week 6 of treatment to week 26; unblinding was a concern of the Committee; and baseline FEV_1 was included as a covariate. • **The Appraisal Committee did not consider mannitol to represent a step-change in treatment.** Therefore it does not meet one criterion for early access to the NHS of interventions that might be innovative. • **Treatment with mannitol will cost about £43,000 per year per 100,000 population.** This is assuming that all patients with cystic fibrosis aged over 18 years of age are prescribed mannitol, in line with its proposed licence as an add-on therapy. It is not clear how many patients will benefit from treatment or how this will affect their lives.	The Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29) It is not within the remit of NICE to consider the financial impact of recommendations on individual PCTs.

Comments received from members of the public

Role*	Section	Comment	Response
288 web comments received from 214 people		Mannitol improves patient lung function, preventing one in four exacerbations. For people with CF this means one less two-week stay in hospital per-year and it will help people with CF, their carers and friends and family, to get on with their lives. It also offers a	The Committee concluded that mannitol is clinically effective in improving both lung function (FEV1) and pulmonary exacerbations in people with cystic fibrosis. The Committee further concluded that

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
contained these statement		potential saving to the NHS as every two-week hospitalisation costs approximately £3,000 per patient. Mannitol is quick and easy to use. Reducing the burden of treatment and care is vital for people with Cystic Fibrosis. As the treatment is delivered through a disposable inhaler it is convenient and hygienic to use, with limited cleaning needed. Mannitol will also help to increase adherence. Because of the huge burden of treatment many people with CF struggle to fulfil their daily medication and physio. Dry powder formulation offers convenience and simplicity. Adhering to the right dose and frequency will ensure maximum efficacy of the treatment. The treatment would be able to benefit a large number of adults with CF as it is effective regardless of mutation, type of infection present or extent of lung disease.	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. (See FAD Section 4.13). NICE must consider a technology's cost effectiveness. Cost savings from reduced need for hospitalisations are fully included in the economic modelling approach. The Committee was aware of the difficulties patients with Cystic Fibrosis face 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. (see FAD Section 4.4) The Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29)

Summary of comments received from members of the public

Theme	Response
Ease of use Convenience: time saved, nebulisers are time consuming to set up and clean, difficult to store	The Committee was aware of the difficulties patients with Cystic Fibrosis face 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. (see FAD Section 4.4)

Theme	Response
(rhDNase requires refrigeration) and travel with, convenience leads to better treatment adherence, discreet and portable Mannitol more tolerable than hypertonic saline: better taste, doesn't burn, easier to administer Mannitol decreases time needed for physiotherapy Younger patients can take care of their own medication Improved job attendance	The Committee concluded that mannitol would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29)
Clinical benefits Lung function: important to preserve and/or improve May be more beneficial for patients with very low lung functions (proportional increases are more important) Effective regardless of concurrent infections Anecdotal evidence of efficacy of mannitol, even if not adequately captured in manufacturer's evidence submission (sputum clearance, long and short term benefits)	The Committee concluded that mannitol is clinically effective in improving both lung function (FEV1) 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. (See FAD 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. (see FAD section 4.27)
Use in practice Perception of replacement, rather than add-on therapy (and therefore treatment burden reduction)	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

Theme	Response
Stopping rule adherence: responsibility of medical management team within PCT to adhere to NICE guidance, with automated messages from Eclipse computer system if patient FEV1 falls outside of recommended range. MMT ensures spending falls within range set by NICE. Prescribing protocols are generally adhered to well. Choice: should be up to patient and/or clinician to decide on appropriate treatments, perception that a NICE no recommendation will completely bar access to mannitol Useful for patients who have limited options after rhDNase	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. See FAD Section 4.3) NICE must consider a technology's cost effectiveness. The Committee 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. (See FAD Section 4.13).
Cost issues Cost effectiveness not adequately captured (benefits underestimated and costs overestimated): costs to wider society and time off work/school not taken into account, represents good value for money Reduced burden on NHS: reduced exacerbation rate, reduced antibiotics prescriptions and IV antibiotics, lung transplants, shorter hospital stays (and less chance for developing further infections which may be antibiotic resistant), prevention is better than cure, other treatments should be deprioritised (cosmetic surgery), costs of long term lung function decrease	The Committee agreed with the manufacturers 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. (See FAD Section 4.22). The NICE methods guide applicable to this appraisal specifies that costs for the NHS and PSS are taken into account. Both, reduced resource use and improved outcomes, as a result of the use of a technology are fully included in the economic modelling approach. The price of a technology is set by the manufacturer and is agreed with the Department of Health.

Theme	Response
Reduction in morbidity and mortality Importance of preventive care for patients NHS should be able to negotiate a lower price Difficult to model CF effectively, with its complicated treatment pathway, leading to underestimation of benefits of mannitol Long term cost-effectiveness data should be established through monitoring of usage in the NHS Cost effectiveness should not be the determining factor (only clinical effectiveness), cost is not an issue, so why has it not been recommended?	NICE must consider a technology's cost effectiveness.
Externalities First new treatment developed since rhDNase Future research: no recommendation would reduce future research, patients have to stay healthy in order to benefit from research (hope for future improvement) Relative youth of CF patients Social and emotional benefits of treatment (benefit to whole family)	NICE considers a technology innovative if a technology has the potential to make a significant and substantial impact on health-related benefits. The criteria used in decision making are outlined in NICEs guide to the methods of technology appraisal (http://www.nice.org.uk/aboutnice/howwework/devnicetech/guidetothemethodsoftechnologyappraisal.jsp) sections 6.1.3, 6.2.9, 6.2.18 -25. Mannitol is licensed for adults only. The Committee agreed with the manufacturers 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. (See FAD Section 4.22)

Theme	Response
Side effects Side effects: increased cough is useful for clearance of sputum, patients are used to side effects of CF treatments Individuals respond differently to different treatments, patients develop intolerance to treatments, important to tailor treatment to individual patients Effects of exacerbations on patients as well as NHS Bronchoconstriction can be dealt with, so should not be a barrier to approval	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 Committee agreed that 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. (See FAD Section 4.11 and 4.20)
Other NHS professional agreed with NICE recommendations, that the improvements are moderate, and that it does not represent a step change in treatment, that there are significant limitations in the trials (power and lack of hypertonic saline as a comparator), that it would cost the specific PCT in the region of £250 000 per annum, which would need to be reallocated from other patients. Support for CF Trust's position: developed over years, based on guidelines Acknowledgment of the limitations of the trials, of the data from the trials, of the manufacturer's submission (regarding hypertonic saline, and lack of model), lack of quality of life evidence: in	Comments noted.

Theme	Response
manufacturer's submission, in the Committee's considerations, too short a timescale to measure long term impacts on quality of life Patients on clinical trials should not lose access Agreement with patient expert on benefits for adherence	
NICE process Time to review is too long Step change that fulfils unmet needs, decreases treatment burden NICE recommendation was based on small technicalities and errors in manufacturer's submission, and has a duty to examine the evidence properly Recommendations for subgroups are unfounded and discriminatory	A review of published guidance can happen at any time if new evidence emerges that would lead to a change in the recommendations. The Committee concluded that mannitol could not be considered an innovative step-change because it would not replace the use nebulisers in cystic fibrosis treatments. (See FAD section 4.29) The Appraisal Committee has examined the evidence submitted by the manufacturer and the review of this evidence thoroughly. (See FAD Evidence Sections 3.1-3.56) Unclear what this ACD comment refers to as no recommendations for subgroups were given in the ACD. The Committee concluded that mannitos was not cost effective for the treatment of all subgroups presented by the manufacturer (some based on the anticipated, but later amended wording of the marketing authorisation, for example people using rhDNase or people who cannot use rhDNase) (see FAD section 4.25), and 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.(see FAD Section 4.26) 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 FEV1% 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. (see FAD section 4.28)