National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, 20 May 2011**. using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Population versus scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that after discussion with NICE it was agreed that there are now two distinct interventions for two separate populations: (1) Mannitol in combination with rhDNase for adults with cystic fibrosis, and (2) Mannitol alone for adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase. See page 6.	Replace “it was agreed that there are now two” with “it was agreed that the ERG would consider the following two”	The final scope (issued August 2010) still refers to “people with cystic fibrosis”. The manufacturer agrees that in discussion with NICE and following the EMA guidance the population would be narrowed down to adults only, but the two distinct populations have never been explicitly discussed.	This was agreed between NICE and the ERG. We are not sure why this is a factual error.

Issue 2 Clinical outcomes reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG mentions several times that “no other data were provided, despite our request for all relevant data for the relevant populations.” See page 6, 37, 44, 105 The ERG states that No data was provided for other outcomes, such as: quality of life and adverse events.” See page 9, 34 The ERG mentions that “Mortality was not assessed in either trial, despite it being mentioned as an	We would like to ask the ERG to remove the four instances where they state “despite our request for all relevant data for the relevant populations." We would also like the ERG to rephrase the sentence on page 9 “No data was provided for other outcomes, such as: quality of life and adverse events.” to "Not all outcomes were reported separately for adult rhDNase users and the adult rhDNase unsuitable population". Idem for page 34. We suggest deleting the sentence about	The ERG did not request additional clinical data for other outcomes. They only requested a cost-effectiveness analysis of both populations. See clarification question A4 bullet 4: “Please could you run the economic model for these two populations separately (mannitol plus rhDNase versus rhDNase plus BSC in all adult CF patients; and mannitol alone versus BSC for CF patients who are ineligible, intolerant or inadequately	See question A4: “... and please provide all the necessary data for the ERG to replicate the economic model in these two populations?” Data provided for the correct populations in the response to the clarification letter were limited to lung function (incomplete: graphs only)

included outcome in the statement of the decision problem" on page 36.	mortality not assessed on page 36. In addition we would like to ask the ERG to replace the NR in table 7 (page 32) for mortality by zero.	responsive to rhDNase) and please provide all the necessary data for the ERG to replicate the economic model in these two populations?" All data for the cost-effectiveness analyses on the 2 populations have been provided to the ERG. The values for mortality and adverse events are reported in table 40 of the MS. The one death occurred in the control arm and was an adolescent.	and exacerbations.

Issue 3 Inconsistencies in reported clinical outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that there are inconsistencies in the data reported in section 5 (page 33 of the ERG report).	We would like to ask the ERG to remove the following sentences on page 33: "There are also inconsistencies in the data reported. In the MS, change in FEV1 is reported as MD=109.27 (52.77, 165.77); in the response to the clarification letter this is: MD=93.95 (NR). In table 30 (MS, page 79), the manufacturer presents data for % predicted FEV1 in adult rhDNase users for both studies and combined. The combined result looks unlikely as the combined mean (2.36) is lower than both means in the two individual studies (2.66 and 2.95, respectively)"	We understand the way it has been presented in the MS can lead to this conclusion, however these are not inconsistencies but relate to difference in the calculations. The MS refers to difference between week 6 and week 26; the CR refers to difference between baseline and week 26 In addition the calculation of % predicted FEV1 in the pooled adult rhDNase users population differed from the calculation for individual study. (see MS table 30 page 80, comment b and d).	With the information we had at the time of writing the report, these looked like inconsistencies. Now that the manufacturer has clarified this issue, there is no need to change the report. We will make sure the text is amended when writing the ERG summary.

Issue 4 Hypertonic Saline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that “Hypertonic saline seems superior in adult rhDNase users” (page 7, 10, 43, 45 and 105) In addition the ERG refers to hypertonic saline as the main comparator. (page 39) Finally the ERG regards the absence of an comparison against hypertonic saline a major weakness (page 8)	We would like to ask the ERG to remove this sentence in the five instances reported. We would like to ask the ERG to remove the words “the main” on page 39. Finally we would like to ask the ERG to remove the word “a major weakness” and replace with “an issue” on page 8.	The ERG themselves concluded that an indirect comparison was not possible with the evidence available, so the superiority conclusion cannot be drawn. Outcomes reported for the mannitol studies are different from the ones reported in the Elkins study, as acknowledged by the ERG report on page 43. In addition for this particular outcome (i.e., exacerbations) the Elkins paper does not report that the age group is non-significant. Elkins only reports that age is non-significant for the linear rate of change in lung function, therefore the suggestion that HS seems superior in the adult population with respect to exacerbation cannot be made. The scope does not say that HS is the main comparator. In conclusion, considering the fact that the ERG themselves had great reservation with the indirect comparison and did not perform a cost-effectiveness analysis against hypertonic saline, we find the	We have explained that our analyses are based on limited evidence and need to be interpreted with caution. This does not look like a factual error, more a difference of opinion.

		qualification this being a major weakness a very strong judgement.	

Issue 5 Model technical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that the model contained various errors (page 9, 91, 92, 95) In addition on page 9 the ERG states that; "It was shown by the ERG that varying this assumption has a major impact on the cost-effectiveness estimate."	We would like to ask the ERG to remove the statement "and the ERG discovered various errors in the model. Although the ERG did its best to find these errors and all errors found were corrected in the ERG's own analyses, this still leaves some questions with respect to the integrity of the model as such." on page 9. In addition we would like to ask the ERG to remove the sentence "It was shown by the ERG that varying this assumption has a major impact on the cost-effectiveness estimate." on page 9.	We acknowledge the point that Table 96 on page 185 in the MS may be misleading, however this is not an error in the model. Due to the chosen cycle length, when stopping the model at _horizon = 1; the model will in fact run for (6+8+12+12+12+12=62 weeks=1.19 year) With regards to the comment on page 9 about respiratory symptoms, no analysis is presented in the ERG report (section 5.3). In addition our analysis, showed that the impact has been tested and was found not to have a great impact on the ICER (see Appendix 18 of MS; Table 125)	We have amended this. We acknowledge that the wording of the ERG in this paragraph of page 9 is slightly ambiguous. Where the ERG writes "…that varying this assumption has a major impact …", we refer to the assumption of maintaining the initial gain in FEV1 % predicted. In 5.3 the ERG has used a shorter time horizon as a proxy to relax this

			assumption. No amendments have been made.
	We would like to ask the ERG to remove the following sentence on page 91: “The average number of life years accumulated in that one year was 1.15. The ERG checked the model to find the source of this error, but in the permitted time frame was unable to locate it.” and page 92: “Finally, the ERG found several errors concerning the parameter values for the distributions used in the PSA.”	With regards to the comment on page 92 of the ERG report we acknowledge we should have reported the N and/or SE. The value reported in table 74 of the MS is the standard deviation. The TreeAge model however uses the correct value (the SE).	The sentence on page 91 is deleted. The remark about errors concerning parameter values did not only relate to the utility variables, but also the utility decrement, duration of an exacerbation and various cost variables. Thus, the sentence on page 92 has not been removed.
	Idem for the comment on page 95, we would like the ERG to remove the sentence “and larger errors, such as the fact that with a time horizon of 1 year, 1.15 life years are accumulated. This is a clear sign that something does not work properly in the model.”		We have amended this.

Issue 6 Systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 18 the ERG concluded that relevant studies might have been missed due to the basic filter employed by the manufacturer. On page 21 the ERG considered it very likely that relevant CE studies may have been missed; however the ERG was unable to screen the additional references due to time constraints.	We would like to ask the ERG to rephrase these sentences that although the filter was not optimal, no relevant studies were missed.	The manufacturer has run the EMBASE search with the RCT filter as suggested by ERG in Table 1. From the 41 identified articles, 20 are reviews on current or future treatments but not referring to any study, 8 were not on CF, 1 was a Cochrane library already considered in the MS (ref 15), 6 concerned tobramycin or other antibiotics, 1 on active studies but it does not provide any outcomes, 4 on MS studies already discussed in the MS and finally one additional review of studies which was relevant (Bolser 2006). Nonetheless, all pertinent studies cited in Bolster 2006 were either already cited in the Cochrane reviews (MS Refs 15, 17) or were MS studies. The manufacturer has run the EMBASE search with the CRD's NHS EED filter mentioned in Table 2 and detailed in Pages 116-117. Of the 14 articles identified in the search, 8 were reviews on current and emergent therapies but none addressed any economic-related issues, 3 were not relevant to CF, 1 was a pipeline of the manufacturer's products, 1 was a Cochrane	Our statement on page 18 is still factually correct as the manufacturer did not screen the ERG's Medline search strategy results for clinical effectiveness (ERG report, 18). The manufacturer's inclusion studies for cost effectiveness were found using a search without a mannitol facet. Their search was structured with a cystic fibrosis facet combined with a cost effectiveness facet. We created a number of new searches using this structure (ERG report, 21-22): Embase – 1136 studies retrieved Medline – 27 studies retrieved Two PubMed searches – 305 and 658 studies retrieved. The manufacturer did not screen the searches detailed above and therefore we cannot state that no relevant studies were missed.

		reference already cited in the MS (MS Ref 15) and finally one was a review (Robertson 2002) citing one study with cost data. This study, Suri et al 2002, was already cited in the MS (Ref 34).	

Issue 7 Minor errors in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report contains some errors on page 6, 7,10, 32, 43, 44, 78, 92, 93, 103, 105, 125	The text on page 7 and 10 should be corrected as follows: The base-case cost-effectiveness results of the manufacturer's submission were originally for rhDNase unsuitable patients (mannitol vs BSC) £41,074/QALY and for the rhDNase users (mannitol + rhDNase versus BSC + rhDNase) patients (mannitol vs BSC) £47,095/QALY.	The ICER figures have been reversed see table 94 MS submission, page 182	Agree, we have amended this
	Table 7 (page 32): "RR = 1.00 (0.61, 1.66); Pooled: RR = 0.44 (0.18, 1.10)" should be replaced by "Pooled: RR = 0.93 (0.57, 1.55); Pooled: RR = 0.45 (0.18, 1.12)." The values in the text on page 6, 43 (Table 12), 44 and 105 of ERG report should be corrected to reflect above numbers.	We checked the performed meta-analysis using CMA software version 2; fixed effects model and derived slightly different values than the one reported in table 7 of the ERG report.	These were the relative risks we obtained using RevMan 5, and using the data that were available to us. No changes made.
	On page 43 (Table 12 as well as text) the confidence interval "(29.02, 159.62)" to be	When recalculating the results of the indirect treatment comparison using	We did use the Bucher method for all our indirect

	replaced by “(-33.67, 222.31)”	the Bucher method (note that the ERG have not indicated which method they used) we get a different confidence interval (Table 12 page 43)	comparisons. We agree that the confidence interval provided by the manufacturer is correct. Page 43 has been amended, as well as the corresponding text on pages 7, 45 and 105..
	On page 78: “From this we found that patients with improved RS symptoms have **97**% of the overall mean costs and patients with no improved RS symptoms **110**%”	It seems the presented % on page 78 are not correct: 4374/4493=97% and 4949/4493=110% of total cost. This would mean table 39 and the analysis would need to be updated as well.	The ERG acknowledges that an error was made when reporting the procedure used to find symptom specific costs. However, the procedure itself is correct. The ERG used table 49 of the response of the manufacturer to the clarification letter. In that table it is presented that 133 patients had no improved RS with mean cost of 4949.3 and 94 patients had improved RS with mean costs of 4373.8. This leads to an overall mean cost estimate of 4710. Then it follows: 4374/4710=93% and 4949/4710=105%. Clearly the discrepancy between the manufacturer suggested percentages and the percentages used by the ERG is explained by the population on which the cost estimation was based. No changes have been made to the report.

	On page 92/93: “According to the ERG, the decrement of 0.23 is found by subtracting 0.61 (SE 0.075) from 0.84 (SE 0.025). The SEs can be derived from the confidence intervals presented in table 73 of the MS. Thus, the overall SE of the decrement is 0.0707. Based on this mean and SE, the parameters of the beta distribution were calculated (a=8.08, b=27.05)” to be replaced by “According to the ERG, the decrement of 0.23 is found by subtracting 0.61 (SE 0.079) from 0.84 (SE 0.028). The SEs can be derived from the confidence intervals presented in table 73 of the MS. Thus, the overall SE of the decrement is 0.0134. Based on this mean and SE, the parameters of the beta distribution were calculated (a=20.63, b=69.08).”	We acknowledge there was a mistake in the parameters estimates as pointed out by the ERG on page 92/93, but when checking the parameter estimates provided by ERG we believe they are not correct either.	Thanks to the correct Bradley reference provided by the manufacturer (last point of this document) it is now clear to the ERG that the CIs reported in the MS are based on a beta distribution. Based on that information we can concur with the manufacturer that the parameter estimates available are 0.61(SE 0.079) and 0.84 (SE 0.028). However, based on these, we derive a SE of the utility decrement of 0.0838, yielding a= 5.8 and b=19.4 as parameters of the beta distribution. This is quite close to the parameters earlier estimated by the ERG, and will thus have little impact on the outcomes.
	On page 103: Table 58 header "RR exacerbation based on rhDNase users adult populations" should be corrected to "RR based on adult subpopulation"		Agree, we have amended this.
	On page 125 remove “and only sparingly	Full details on the linear regression	Agree, we have amended this

	explained, e.g. no residual analysis presented. The regression results in Appendix B of the clarification response suggest a fixed effect model to be more appropriate."	were presented in Appendix 14 of the MS, including residual analysis (Figure 26 and 27). In addition Appendix B of the CR refers to the Poisson regression for the PDPE rate ratio.	

Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG points out the Bradley reference is incorrect (page 73, 125)	No amendment needed	Although the ERG did not request a clarification on this point, we here provide the correct reference for completeness: Bradley J, Blume S, Stafford M, Balp M, Elborn S. Quality of life and utility in patients with cystic fibrosis. Presented at European Respiratory Society (ERS) Annual Congress, 2010 18-22 Sep; Barcelona, Spain. 2010.	Thank you!