Dear Jeremy,

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 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 FEV1 predicted rather than the primary outcome of the trials, absolute FEV1.

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 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 FEV1 from baseline to week 26 to

change from week 6 of treatment to week 26; unblinding was a concern of the committee; and baseline FEV1 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 (FEV1) from baseline to week 26. The manufacturer stated that this was changed to change in absolute FEV1 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 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 FEV1 response, respiratory symptoms, adverse events or health-related quality of life for the two rhDNase subgroups.

If you require any further information please contact me directly by phone [redacted] or email [redacted]@sandwell-pct.nhs.uk.

PS Can you please confirm that you have received this submission?

Yours sincerely

[redacted]
Sandwell PCT
Kingston House
438, High street, West Bromwich B70 9LD

Telephone [redacted]

Mobile [redacted]
Fax [redacted]
E-mail [redacted]@sandwell-pct.nhs.uk
E-mail [redacted]@nhs.net (secure)