csas
Commissioning Support
Appraisals Service

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11th June 2012

National Institute for Health and Clinical Excellence

Dear Jeremy,

RE: Mannitol dry powder for inhalation for the treatment of cystic fibrosis

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 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 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.

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- **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.

If you require any further information please contact me directly: Phone: [redacted], email [redacted]@sph.nhs.uk.

Yours sincerely

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