NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Diana Bilton

Name of your organisation Royal Brompton & Harefield NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

  Chair of Clinical Reference Group for Specialist Commissioning of Cystic Fibrosis.

  Chair of Medical Advisory Group of UK CF Trust

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

CYSTIC FIBROSIS is managed via specialist centres with an extended network of clinics in paediatrics linked to specialist centres. Care is delivered by a multidisciplinary team.

The overall theme of management involves ensuring 1) adequate airway clearance of abnormal secretions by physical means (ie. physiotherapy) enhanced by inhaled therapies (ie. rhDNase); 2) An antibiotic regimen that suppresses growth of the bacteria (eg. nebulised anti-Pseudomonal antibiotics); 3) Suppression of inflammation associated with infection eg. use of Azithromycin long term in patients with chronic Pseudomonas infection. These strategies are designed to maintain lung function and reduce pulmonary exacerbations.
There are standards of care produced by the UK CF Trust. Variation in care occurs in the UK related to differences in funding. It is worth noting that despite a European consensus that all people with CF over 5 years of age should be offered therapy with rhDNase only 42.7% of patients on the UK CF Registry receive this medication (UK CF Registry Annual Report 2010).
The landscape will change as CF is one of the specialist conditions to come under National Specialist Commissioning. Work is in progress to agree a National Service Specification and a commissioning policy for CF specialist medicines.
<u>Alternatives to Mannitol</u>
Mannitol is a hyperosmolar agent and has an additive effect to rhDNase in the clinical trials in terms of improvement in pulmonary function. rhDNase acts as a mucolytic by clearing the DNA debris from dead neutrophils left in the airway. Thus mannitol

and rhDNase are working via alternate paths to enhance airway clearance and reduce exacerbations.
The alternative hyperosmolar agent is hypertonic saline (HS). This requires nebulisation and although the original paper (Elkins NEJM 2006) studied 7% HS there is significant variation in the concentration used in clinical practice.
The major advantage of mannitol relates to the dry powder inhaled formulation. The burden of treatment is an important issue for CF care currently. Our aim is to keep people with CF at school, college and work, hence the drive to minimise the burden of nebulised therapy whilst ensuring efficacy. Thus as mannitol shows efficacy regardless of use of rhDNase it represents a further choice for patients who may not be able to fit the regimen of nebulised therapies and nebuliser cleaning in to the busy daily schedule.
Setting
Inhaled mannitol would be initiated by the specialist centre team with appropriate education from the CF physiotherapist on inhaler use. This is standard practice for any inhaled therapy in CF care. No additional professional input is required.
Guidelines
Mannitol has not yet been considered in CF pulmonary therapy guidelines as these all predated the results of the trials.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Inhaled mannitol represents the first agent that improves airway clearance available as an inhaled rather than nebulised therapy. People with CF are increasingly seeking to reduce the burden of nebulised therapies.
The therapy requires a test dose and anyone failing the test (ie. suffering bronchoconstriction) will not continue on therapy. Furthermore it is clear that people with CF and the clinicians will stop therapy if there is lack of efficacy (ie. no change in lung function).
One of the trials was conducted in UK patients (Bilton et al, ERJ 2011) and thus the results would be expected to be similar in UK practice.
The key outcomes of reduction in exacerbations and improvement in lung function represent critical determinants of long term survival in these patients. Furthermore exacerbations represent an important outcome for patients in terms of a negative impact on quality of life and disruption of studies or work.
The side effect which is immediately evident is bronchoconstriction. This would preclude further use. There is no evidence in the trial data of emergence of this side effect.
Long term surveillance is required post marketing to ensure haemoptysis is monitored.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra facilities or equipment are required. Physiotherapists are already trained to check for bronchoconstriction after first dose of nebulised therapies in CF

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