National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

Response to consultee and commentator comments on the draft remit and draft scope (2nd consultation)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Association of Respiratory Nurse Specialists	Accurate reflection of the general effect of CF & some of its treatments for the lung disease aspect of CF.	Comment noted.
	Cystic Fibrosis Trust	Satisfactory.	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Nursing	Background information is comprehensive. We would add that symptoms of CF also include CF related diabetes in some patients, male infertility and liver involvement in some patients. Other comparators could also include an oral mucolytic known as acetylcysteine. We are not sure about the claim that 56 of the 97 deaths from CF in UK were due to pulmonary manifestations – one would have thought it would be a higher number – a reference for this would be helpful.	Comment noted. These conditions have been added to the background section of the scope. Following the scoping exercises and scoping workshop, it was agreed that the following comparators are appropriate: rhDNase, nebulised hypertonic saline, and best supportive care (which may include a wide range of inhaled and oral active treatments). Oral acetylcysteine could therefore be included within the definition of best supportive care. This figure is from the National Horizon Scanning Centre document: http://www.haps.bham.ac.uk/publichealth/horizon/outputs/documents/2008/april/Bronchitol.pdf
	Royal College of Paediatrics and Child Health	Yes.	Comment noted.

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	Pharmaxis	The background provided in the draft scope by NICE is accurate in our view. *(Full comment not reproduced here)* 1. Impaired mucociliary clearance plays a pivotal role in disease progression. *(Full comment not reproduced here)* 2. Inability to clear mucus causes significant morbidity and mortality. *(Full comment not reproduced here)* 3. There remains a large unmet medical need. *(Full comment not reproduced here)* 4. Treatments. *(Full comment not reproduced here)* 5. Non-compliance is an important issue. *(Full comment not reproduced here)*	Comment noted. The scope is intended to be a brief summary document and the appraisal will fully consider the clinical and cost effectiveness of the technology in line with the NICE reference case. No changes have been made to the scope.
The technology/ intervention	Cystic Fibrosis Trust	Yes.	Comment noted.
	Royal College of Nursing	This seems accurate.	Comment noted.
	Royal College of Paediatrics and Child Health	Yes.	Comment noted.

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	Pharmaxis	What is Bronchitol? Bronchitol has been subject to a 10 year pharmaceutical, preclinical and clinical development program and is covered by patents granted in most major jurisdictions. Bronchitol is precision spray dried mannitol manufactured to form hollow spheres with a mean particle size of 3 microns, encapsulated in gelatine capsules and delivered via an easy to use dry powder inhaler. The production process developed by Pharmaxis is carefully controlled to deliver a narrow range of particle size. The combination of this tight specification and the dry powder inhaler enables distribution of substantial doses to the large and small airways where mucus build up is a significant cause of morbidity and mortality. Formulation of an osmotic substance in a respirable dry powder represents a significant breakthrough since the load required to generate a significant osmotic effect in the lung can be delivered in about 2-5 minutes which is a vast improvement on the many nebulised drugs that CF patients currently take. How does Bronchitol work? *(Full comment not reproduced here)* Patient benefits of Bronchitol .... Bronchitol can be delivered in 2-5 minutes by a simple hand held inhaler similar to those used to deliver asthma medications. It is intended that each patient will receive one new inhaler per week and that there will be minimal need for cleaning and no maintenance. *(Full comment not reproduced here)*	Comment noted. The scope is intended to be a brief summary document and the appraisal will fully consider the clinical and cost effectiveness of the technology in line with the NICE reference case. No changes have been made to the scope.
Population	Association of Respiratory Nurse Specialists	Definition & no.s seems appropriate.	Comment noted.
	Cystic Fibrosis Trust	The population is defined appropriately. There are no groups that should be considered separately.	Comment noted.

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	Royal College of Nursing	The population is appropriately defined – the majority of those with CF and chest symptoms could benefit from this treatment, especially those with thicker and sticker mucus which is hard to shift.	Comment noted.
	Royal College of Paediatrics and Child Health	Yes. However, we note that the lower age limit of 6 years is usually set because of the feasibility of performing spirometry. We think that all new interventions for CF need to be considered for younger populations as lung disease starts in preschool children.	Comment noted. The appraisal will be conducted in accordance with the marketing authorisation.
	United Kingdom Clinical Pharmacy Association	Dependent upon the design of clinical trials, including those yet to be reported, and the future marketing application. It may be necessary to consider separately those patients under or over 18; and separate groups dependent upon their pre-existing lung function as measured by FEV.	Comment noted. Subgroup analysis based on lung function has been added to the other considerations section. The NICE Social Value Judgements document (http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf) states that where age is an indicator of benefit or risk, it can be taken into account. No evidence to suggest that age is an indicator of risk and benefit was identified during the scoping exercises or at the scoping workshop and therefore no changes have been made to the scope.

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	Pharmaxis	..... predicting a more clinically effective or cost effective sub-group has not been established. The enrolment challenges of such a rare disease and the mechanism of action are such that reliably identifying a specific sub-group who would not respond is unlikely. An alternative approach would be to establish which patients do not adequately respond to treatment after a trial period. This is currently explored as part of the analysis of the pivotal study CF301. *(Full comment not reproduced here)*	Comment noted. The scope is intended to be a brief summary document and the appraisal will fully consider the clinical and cost effectiveness of the technology in line with the NICE reference case. No changes have been made to the scope.
Comparators	Association of Respiratory Nurse Specialists	RhDnase & nebulised hypertonic saline thin secretions, whereas Mannitol hydrates the airways as well as thinning secretions & inducing cough stimulus, to increase expectoration	Comment noted.
	Association of Respiratory Nurse Specialists	I feel the comparators using Dnase and Hypertonic Saline are appropriate.	Comment noted.
	Cystic Fibrosis Trust	CF health is achieved by the use of a large range of drugs, each of which may be improving lung function by 3% - 5%. Cumulatively, they are all important. Some patients respond better to some drugs than others, so doctors need an “armoury” of treatments to ensure the best possible outcomes.	Comment noted.

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	Royal College of Nursing	As above, an oral mucolytic (acetylcysteine) could be included in comparators. Otherwise, the list is comprehensive. We are unaware of the cost of the mannitol therapy (and have not been able to find this out), but would imagine it will be less than rhDNase and more than hypertonic saline.	Following the scoping exercises and scoping workshop, it was agreed that the following comparators are appropriate: rhDNase, nebulised hypertonic saline, and best supportive care (which may include a wide range of inhaled and oral active treatments). Oral acetylcysteine could therefore be included within the definition of best supportive care.
	Royal College of Paediatrics and Child Health	Yes.	Comment noted.
	United Kingdom Clinical Pharmacy Association	At this time rhDNase and hypertonic saline solutions for nebulisation are the appropriate comparator products. Ideally, inhaled mannitol should be compared separately, and in combination with rhDNase, hypertonic saline and the combination of both products.	Comment noted. The scope allows for these treatments to be used alone or in combination with each other.

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	Pharmaxis	The most appropriate comparator for NICE's appraisal of Bronchitol is usual or standard care which is as per the placebo groups in the clinical trials being performed to support an application for a marketing authorisation in Europe. *(Full comment not reproduced here)* ....NICE proposes that hypertonic saline and rhDnase should be used as comparators, in addition to best supportive care, for this appraisal. Pharmaxis believe that best supportive care/standard of care is the ideal comparator and propose that hypertonic saline and rhDnase should not be considered as comparators... *(Full comment not reproduced here)* So in summary: 1. Current patient management involves the use of multiple therapies such as bronchodilators, steroids, physiotherapy, antibiotics, hypertonic saline and rhDNase. 2. Bronchitol is targeted as a second line treatment to be added onto rhDNase or where rhDNase is not a viable option and hence cannot be a comparator. 3. Hypertonic saline is not an approved treatment and is most widely used at dosages that have not been proven effective. It would not be an appropriate comparator. Hence the most appropriate comparator would be usual or standard care which is as per the placebo groups in the clinical trials being performed to support an application for a marketing authorisation in Europe.	Comment noted. Following the scoping exercises and scoping workshop, it was agreed that the following comparators are appropriate: rhDNase, nebulised hypertonic saline, and best supportive care (which may include a wide range of inhaled and oral active treatments). The scope is intended to be a brief summary document and the appraisal will fully consider the clinical and cost effectiveness of the technology in line with the NICE reference case. No changes have been made to the scope.
Outcomes	Association of Respiratory Nurse Specialists	Yes	Comment noted.

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	Association of Respiratory Nurse Specialists	I feel the outcome measures will capture the most important health related benefits.	Comment noted.
	Cystic Fibrosis Trust	Yes. The outcomes listed are appropriate.	Comment noted.
	Royal College of Nursing	The outcome measures mentioned seem appropriate.	Comment noted.
	Royal College of Paediatrics and Child Health	Yes.	Comment noted.
	United Kingdom Clinical Pharmacy Association	Mortality is unlikely to be a useful outcome measure over the length of any clinical trials submitted. Maintenance and/or improvement in lung function coupled with a reduction in respiratory symptoms or an improvement in health-related quality of life represent the best outcome measures. Perceived or measured adverse effects are also a useful outcome. Effects on exercise tolerance are only a useful outcome measure if they can be directly measured and compared to the effects of existing treatments.	Comments noted. Mortality has been included as a clinically relevant outcome. Data informing estimates of life expectancy would be expected to be incorporated in the economic model.
	Pharmaxis	Although we have not planned a direct mortality study (not considered feasible), extending life expectancy is an important outcome in CF. Lung functioning (FEV1 and FVC) has been shown to be predictive of mortality [Stern et al; 2008, Hayllar et al; 1997, Courtney et al; 2007]. We have commissioned research from a global-leading health statistics group to review data held in one of the world-wide CF Registry databases. An additional important outcome measure to be considered is reduction in pulmonary exacerbations. Exacerbations associated with infections typically worsen the progression of lung disease in these patients. *(Full comment not reproduced here)*	Comment noted. The scope is intended to be a brief summary document and the appraisal will fully consider the clinical and cost effectiveness of the technology in line with the NICE reference case. No changes have been made to the scope.

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Economic analysis	Royal College of Nursing	If this treatment reduces the number of chest exacerbations, need for intravenous antibiotics and hospital admissions then it could be economically beneficial to the CF population. We do not have information on the cost, therefore, are unable to comment at this stage on the proposed cost of this treatment.	Comment noted.
	Royal College of Paediatrics and Child Health	Appropriate.	Comment noted.
	United Kingdom Clinical Pharmacy Association	As the product has not been granted marketing authorisation the costs will presumably be unknown.	Comment noted. The economic analysis will follow the NICE reference case.
	Pharmaxis	In addition to looking at incremental cost/QALY we believe that it is relevant to assess the incremental costs per life year gained. The according time horizon we propose is life long. Resource use and the reduction of exacerbations will be addressed in the economic analysis.	Comment noted.
Equality and Diversity	Association of Respiratory Nurse Specialists	My only concern could be the risk of post code prescribing, if the prescribing of the medication is dependent on commissioners funding the medication. Especially with the proposed payment by results commissioning plans.	NICE guidance helps to standardise access to healthcare across the country. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals.
	Royal College of Nursing	This appears to be a simple technology, which the majority of people should be able to use. If the cost of the therapy is within reason, there would be no reason for it not to be used in preference to rhDNase which remains expensive.	Comment noted.

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	Pharmaxis	Bronchitol can be delivered in 2-5 minutes by a simple hand held inhaler similar to those used to deliver asthma medications. It is intended that each patient will receive one new inhaler per week and that there will be minimal need for cleaning and no maintenance. Transporting and administering Bronchitol should therefore not interfere with patient's activities at school, university, work, family holidays, etc. There are two issues that may prevent equal access to the technology: • It is possible that patients with physical disabilities that reduce their manual dexterity and make it difficult to load capsules into the inhaler might not be able to use Bronchitol without assistance. • Very young children under 6 may not be able to generate sufficient inspiratory flow to operate the inhaler.	Comment noted. Consideration will be given to people with a disability who may not be able to manipulate inhaler devices.
Other considerations	Cystic Fibrosis Trust	It is important that quality of life as well as length of life is included in the appraisal.	Mortality and health-related quality of life are both included as outcomes in the scope.
	Royal College of Nursing	Quality of life measures are important outcome – if the treatment is simple and acceptable to take, adherence levels will increase. It would appear that the hand held inhaler device will be easier and quicker to use than the current nebulised alternative options (rhDNAse and hypertonic saline). It may also be more palatable to take than hypertonic saline, as the taste at the back of the throat is more acceptable (this is a common complaint from those patients taking hypertonic saline). From the studies done, it would appear that mannitol is safe to take and well tolerated with minimal adverse events (Chest, 2008; Respirology, 2005). Although there are several papers regarding the benefits of inhaled mannitol in non-CF conditions (eg. Bronchiectasis), there probably needs to be further independent research into the benefits of mannitol in CF.	Comment noted.

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	Royal College of Paediatrics and Child Health	Further research in younger subjects.	Comment noted. The appraisal will be conducted in accordance with the marketing authorisation.
Questions for consultation	Association of Respiratory Nurse Specialists	An alternative treatment for those who have been unable to tolerate RhDnase or hypertonic saline in the past. Wills PJ (2007) Inhaled Mannitol in Cystic Fibrosis In : Expert opinion on Investigational Drugs Jaques A (2008) Inhaled Mannitol improves lung function in Cystic Fibrosis. In: Chest 2008 Daviskas E (2008) Effect of increasing doses of Mannitol on mucus clearance in patients with Bronchiectasis In: European Respiratory Journal D Bilton (2010) Phase III study of inhaled dry powder mannitol (Bronchitol) in cystic fibrosis – results from the 6 and 12 month open label phase Journal of Cystic Fibrosis	Comment noted. The appraisal will be conducted in accordance with the marketing authorisation. If evidence allows subgroup analysis by prior treatment (including consideration of intolerance to treatments) should be considered.

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	Association of Respiratory Nurse Specialists	Would manitol be an add-on treatment or in place of other treatments?	Comment noted. The appraisal will be conducted in accordance with the marketing authorisation. If evidence allows subgroup analysis by prior treatment (including consideration of intolerance to treatments) should be considered.
	BritishThoracic Society	My main concern is whether this treatment will be used in addition to other inhaled therapies or instead of them. Is there sufficient trial data to say whether inhaled mannitol has a beneficial effect in addition to current treatment which may include nebulised hypertonic saline and nebulised pulmozyme. If inhaled mannitol is going to be in addition to current inhaled treatment then what is the cost/ benefit?	Comment noted. The appraisal will be conducted in accordance with the marketing authorisation. If evidence allows subgroup analysis by prior treatment (including consideration of intolerance to treatments) should be considered.

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	United Kingdom Clinical Pharmacy Association	What are the measurable benefits of inhaled mannitol in those patients: (a) not using other inhaled mucoactive agents (b) using rhDNase (c) using nebulised hypertonic saline (d) using both rhDNase and nebulised hypertonic saline Are the same benefits apparent in those patients: (a) under 18 years of age (b) over 18 years of age (c) with varying degrees of pre-existing lung function Is the dry powder device usable by all groups of patients or are there certain groups in whom the technology will not be usable (children, those with reduced manual dexterity)	Comment noted. Subgroup analysis based on lung function has been added to the other considerations section. The NICE Social Value Judgements document (http://www.nice.org.uk/media/998/50/SVJ2ForPublicConsultation.pdf) states that where age is an indicator of benefit or risk, it can be taken into account. No evidence to suggest that age is an indicator of risk and benefit was identified during the scoping exercises or at the scoping workshop and therefore no changes have been made to the scope. The appraisal will give consideration to people with a disability who may not be able to manipulate inhaler devices.

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	Pharmaxis	We consider the most relevant outcome measures to be considered should include lung function, mortality and reduction in pulmonary exacerbations. (See complete response under OUTCOMES and TECHNOLOGY) The pivotal study CF301 explored the effect of Bronchitol on top of standard care, The results of study CF301 demonstrated an improvement in lung function (as measured by change in FEV1 over 26 weeks) and this benefit was seen irrespective of concurrent rhDNase use [Bilton et al; 2009]. Furthermore, the open-label extension phase confirms that the benefits seen over 26 weeks were sustained out to 18 months. These data will be used to support the benefit of Bronchitol compared to standard care.	Comment noted.
	Pharmaxis	We believe the timing of the scoping meeting is appropriate. We filed a submission for marketing authorisation to the EMA late last year. Therefore we believe it appropriate that the NICE review should facilitate equal access to this new drug as quickly as possible after the marketing authorisation has been granted. . The NICE Single Technology Appraisal process triggered for Bronchitol precedes marketing authorization approval expected early next year. In an effort to accommodate this tight schedule Pharmaxis will work towards providing tentative costs of Bronchitol required in Section A of the submission. The final acquisition costs and target population are contingent on the final label text approved by EMA	Comment noted.
Additional comments on the draft scope.	Royal College of Physicians	The RCP wishes to endorse the comments submitted by the BTS on this draft scope consultation.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Welsh Assembly Government
Sandwell PCT
NHS Quality Improvement Scotland
Public Health Wales NHS Trust