mannitol, 400mg, inhalation powder, hard capsule (Bronchitol®)  
SMC No. (837/13)

Pharmaxis Ltd.

11 January 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Are Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**mannitol (Bronchitol®)** is not recommended for use within NHS Scotland.

**Indication under review:** Treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

In two phase III clinical studies in patients with CF, inhaled mannitol was superior to a control treatment (a sub-therapeutic dose of inhaled mannitol) measured by absolute change in forced expiratory volume in one second (FEV₁) over 26 weeks.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,  
Scottish Medicines Consortium
### Indication
Treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

### Dosing Information
The recommended dose is 400 mg twice a day. This requires the inhalation of the contents of ten capsules via the inhaler device twice a day. The therapeutic dose regimen should not be prescribed until the initiation dose assessment has been performed.

For patients receiving several respiratory therapies, the recommended order is:
1. Bronchodilator (must be administered 5-15 minutes before mannitol).
2. Mannitol
3. Physiotherapy/exercise
4. Dornase alfa (if applicable)
5. Inhaled antibiotics (if applicable)

Before commencing treatment with mannitol, all patients should be assessed for bronchial hyper-responsiveness to inhaled mannitol during administration of their initiation dose.¹

### Product availability date
28 May 2012

Inhaled mannitol was designated as an orphan medicine in November 2005.

### Summary of evidence on comparative efficacy
Cystic fibrosis (CF) is a life-limiting, recessively-inherited disease, which affects approximately 9000 patients in the UK. There is a high unmet need for new, effective treatments for CF. The aim of treatment in CF is to improve quality of life and extend life expectancy.² Inhaled mannitol is a hyperosmotic agent intended to facilitate clearance of mucus by ciliary and cough action. Its exact mechanism is unknown but it is thought to act by increasing the hydration of the periciliary fluid layer and by changing the viscoelastic properties of mucus.¹,³

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers inhaled mannitol as an add-on to best standard of care in adult patients with CF who are not currently using dornase alfa (rhDNase) due to lack of response or intolerance. This is a narrower population than that covered by the licensed indication, which includes adult patients with CF. This sub-population of adult patients (referred to as rhDNase non-users) are at an increased risk of experiencing exacerbations, which in turn is associated with an accelerated decline in lung function and further exacerbation events that can result in an early lung transplantation and/or death. This group of rhDNase non-users is considered to have a significant unmet medical need, with current therapeutic options for airway clearance being exhausted by the time of adulthood.
The evidence to support the use of inhaled mannitol derives from two similarly designed phase III randomised, double-blind, controlled clinical studies in patients aged ≥6 years with CF. Patients recruited to the studies had a confirmed diagnosis of CF and a forced expiratory volume in 1 second (FEV$_1$) of ≥30% to <90% predicted at baseline in study DPM-CF-301 (study 301), and ≥40% to <90% in study DPM-CF-302 (study 302). Use of nebulised hypertonic saline was not permitted, but all other treatments were continued, including dornase alfa if prescribed at baseline. Patients were randomised in a 3:2 ratio to receive inhaled mannitol 400mg twice daily or a control treatment, which was a sub-therapeutic dose of inhaled mannitol (50mg) twice daily. The primary outcome was the absolute difference in FEV$_1$ averaged over the 26-week double-blind phase of the study, analysed using a mixed model repeated measures method. After completion of the double-blind phase, patients could enter a 26-week open-label extension phase, during which all patients received inhaled mannitol 400mg twice daily.

Study 301$^4$ included 295 patients in the intention-to-treat (ITT) population (177 in the inhaled mannitol 400mg group and 118 in the control group). The absolute difference in FEV$_1$ averaged across all post-randomisation visits (weeks 6, 14 and 26) in the double-blind phase of the study for mannitol-treated patients compared with control was 85ml (95% confidence interval [CI]: 53ml to 117ml; p<0.001). The effect was similar and statistically significant for both the subgroups of patients receiving dornase alfa (85ml; 95% CI: 43ml to 128ml) and patients not receiving dornase alfa (85ml; 95% CI: 38ml to 131ml). In study 302$^5$, 305 patients were analysed in the ITT population (184 in the inhaled mannitol group and 121 in the control group). The absolute difference in FEV$_1$ averaged across all post-randomisation visits (weeks 6, 14 and 26) in the double-blind phase of the study for mannitol-treated patients compared with control was not statistically significant at 54ml (95% confidence interval [CI]: -2ml to 110ml; p=0.059). The between-group difference in FEV$_1$ in patients using dornase alfa at baseline (43ml; p<0.177) and in patients not using dornase alfa (87ml; p=0.12) was not statistically significant. In the pooled studies, the incidence of exacerbations and associated rescue antibiotic use was reduced by 29% (relative risk 0.71, 95% CI: 0.51, 0.98, p=0.039) and 30% (relative risk 0.70, 95% CI: 0.50, 0.97, p=0.033), respectively in the mannitol group compared to control.

### Table 1. Results of the primary outcome for studies 301 and 302

<table>
<thead>
<tr>
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<th>Study 301 (N=295)</th>
<th>Study 302 (N=305)</th>
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</thead>
<tbody>
<tr>
<td>Absolute difference in FEV$_1$ over 26 weeks (ITT population)</td>
<td>85mL (95% CI 53mL to 117mL)</td>
<td>54mL (95% CI: -2mL to 110mL)*</td>
</tr>
<tr>
<td>Absolute difference in FEV$_1$ over 26 weeks (dornase alfa users)</td>
<td>85mL (95% CI 43mL to 128mL)</td>
<td>43mL (95% CI not reported)*</td>
</tr>
<tr>
<td>Absolute difference in FEV$_1$ over 26 weeks (dornase alfa non-users)</td>
<td>85mL (95% CI 38mL to 131mL)</td>
<td>87mL (95% CI not reported)*</td>
</tr>
</tbody>
</table>

*Not statistically significant

Quality of life was measured in both studies using the age-appropriate Cystic Fibrosis Questionnaire-Revised (CFQ-R). In study 301, the results from the CFQ-R treatment burden domain were similar at baseline and at the end of the study, but there was a significant difference in the mean change from baseline (3.8 points) in the respiratory score in favour of mannitol.$^4$ A difference of 4 or more points in the respiratory score is considered to be clinically
meaningful. In study 302, there was no significant difference in quality of life from baseline for either treatment group, or between treatment groups, for any of the quality of life domains.\textsuperscript{9}

The company presented results for the sub-group of adult patients which represents the licensed population, and non-users of dornase alfa, the proposed positioning. However, these results have not been published elsewhere so could not be verified.

In a pooled analysis of adult patients from both studies (n=341), the mean absolute difference in FEV\textsubscript{1} for mannitol-treated patients compared with control was 100mL (95% CI: 49mL to 150mL; \(p<0.001\)). In the pooled sub-group analysis of adult patients who were non-users of dornase alfa (n=134), the mean absolute difference in FEV\textsubscript{1} in this sub-population for mannitol-treated patients compared with control was 110mL (95% confidence interval [CI]: 30mL to 191mL; \(p=0.007\)).

**Summary of evidence on comparative safety**

No comparative safety data are available.

Patients require screening for airway hyper-responsiveness to inhaled mannitol before commencing treatment.\textsuperscript{1} In both pivotal studies, 7% of patients failed the mannitol tolerance test.

Inhaled mannitol has been associated with respiratory adverse events including cough, haemoptysis and pharyngolaryngeal pain, and gastro-intestinal events, most commonly abdominal pain.\textsuperscript{3}

In both studies, the proportion of patients who experienced any adverse event (AE) or any serious adverse event (SAE) was similar in the inhaled mannitol and the control groups.

In study 301, treatment-emergent AEs that were reported more commonly in the inhaled mannitol group than the control group included cough (25% versus 20%), haemoptysis (12% versus 9%) and pharyngolaryngeal pain (14% versus 4%). Lower respiratory tract infection was reported less frequently in the mannitol group than in the control group (8% versus 17%).

In study 302, treatment-emergent AEs occurring in \(\geq 5\%\) of patients included 'condition aggravated' (41% in the inhaled mannitol group versus 45% in the control group), headache (14% versus 18%), cough (15% versus 13%) and pharyngolaryngeal pain (10% versus 11%). Upper respiratory tract infection was reported less frequently in the mannitol group than in the control group (5% versus 9%).

Safety results from the pooled studies of the incidences of SAEs in dornase alfa users versus dornase alfa non-users were reported in the European Medicines Agency’s CHMP assessment report.\textsuperscript{3} More SAEs were experienced by dornase alfa users (25% versus 28% for the inhaled mannitol and control groups respectively) than dornase alfa non-users (15% versus 25%) in both treatment groups. The most commonly reported event was 'condition aggravated', which occurred in 21% versus 19% for the inhaled mannitol and control groups respectively, in dornase alfa users, and in 9% versus 19% respectively in dornase alfa non-users.\textsuperscript{3}
**Summary of clinical effectiveness issues**

The evidence to support the marketing authorisation for inhaled mannitol was derived from two similarly designed phase III randomised controlled, double-blind clinical studies in children aged ≥6 years and adults with CF. The marketing authorisation granted, however, includes adults aged ≥18 years only. The submitting company has requested that SMC considers inhaled mannitol as an add-on to best standard of care in adult patients with CF who are not currently using dornase alfa. This represents a very small proportion of the study population. The proportion of the pooled study population who were adults not using dornase alfa was 22% (n=134). It is acknowledged by the company that the statistical power to detect a treatment difference in this patient group is substantially reduced.

The company has suggested that there is an unmet need for an effective treatment in patients who have failed to respond to, or are intolerant of, other treatments, including hypertonic saline and dornase alfa. However, it is unclear whether the patients who were non-users of dornase alfa in the pivotal studies had previously tried this treatment.

The company submitted the results of sub-group analyses in adults aged ≥18 years of the two pivotal phase III clinical studies; however, these results have not been published elsewhere so could not be verified.

Only one of the two studies (study 301) reached statistical significance for the primary endpoint. There was no significant difference in protocol-defined pulmonary exacerbations in either study. There was a high drop-out rate in both studies (30% in study 301 and 15% in study 302). Therefore, there remains uncertainty about the robustness of the study results.

The primary outcome was change in FEV₁ measured at 26 weeks; the effectiveness of inhaled mannitol in treating cystic fibrosis over a longer time-period remains uncertain.

There are no studies directly comparing inhaled mannitol with other mucolytic therapies for CF (dornase alfa or hypertonic saline).

Inhaled mannitol offers an alternative licensed therapy for cystic fibrosis, which is a life-long, incurable condition, with a high unmet need for effective therapies. Inhaled mannitol has been designated an orphan medicinal product. It is administered as a dry powder inhalation, so may offer an important advantage over alternative treatments which require nebulisation. Patients require screening for airway hyper-responsiveness to inhaled mannitol before commencing treatment. In the pivotal studies, 7% of patients failed the mannitol tolerance test.

**Summary of comparative health economic evidence**

The company submitted a lifetime cost-utility analysis of adding inhaled mannitol to ‘usual care’ for adult patients with cystic fibrosis; the proposed positioning is for use in people who have not responded to or cannot tolerate dornase alfa (rhDNase).

To estimate efficacy parameters in the model, the company carried out modelling work on patient data from a registry study in Australia that followed up people with CF over time in order to estimate effects over a patient’s lifetime. On this basis, the company estimated the rate of change of lung function (as measured by change in FEV1 % predicted) and exacerbations as a
function of factors such as age, baseline FEV1, and BMI. The results from this analysis were then taken to represent the natural history and resource use of Scottish patients over time. This included estimates of the chance of a lung transplant when FEV1 fell below 30% of predicted, and the chance of a patient dying of CF or of another cause. Data from the clinical trials on how inhaled mannitol would alter this natural history in terms of rate of change of lung function and the rate of exacerbations were then applied, and estimates derived of changes in time spent alive with CF on different treatments, exacerbations, transplants and survival.

Data on quality of life were taken from several sources. The Health Utilities Index, mark 2 (HUI-2 index) was used in the clinical trials but this gave high utility values (around 90% of perfect health at baseline) and there was little change over the duration of the trial or between treatment groups. This was explained on the basis that patients with CF adjusting their quality of life expectations self-report few problems. The company used this value for time alive with CF when FEV1 was over 30% of predicted and the patient was not suffering an exacerbation. For exacerbation and transplant utility, data from previously published research was used.

For resource use, data were taken from the pooled clinical trials and included a full range of costs for CF care including prescribing, community services and hospital services. These were used to derive a cost for ‘routine care’ and a cost for exacerbations; the latter was obtained by comparing costs in the trial for patients who did and did not have an exacerbation.

The company base case estimates were that, over the lifetime of the patient, inhaled mannitol:

- Increased discounted net costs by £10,870 (£192,006 versus £181,135)
- Increased discounted life-years by 0.56 (11.73 versus 11.17)
- Increased discounted quality adjusted life years (QALYs) by 0.52 (10.35 versus 9.83)

The net cost per QALY gained was thus £20,736.

The sensitivity analysis presented in the submission showed no important differences in the cost per QALY for the majority of changes to the base case considered, and a probabilistic sensitivity analysis carried out by the company suggested that the chance that the cost per QALY was less than £30k was 81.8%. One of the few scenarios where the cost per QALY rose above £30k was when the time horizon of the analysis was limited to 5 years (£48k per QALY) since the long term benefits of treatment would be truncated.

One of the main issues with the case presented was the extent of extrapolation from the pooled clinical trials required to obtain the stated cost per QALY. The company’s economic model predicts that on average using inhaled mannitol adds at least 6 months to survival, and that for most patients the quality of life in these extra six months is 90% of normal. Whether this can be supported by the clinical evidence base is a source of uncertainty.

In converting the clinical evidence base into the estimated survival and QALY benefit, the submission includes number of decisions and assumptions that can be seen as weaknesses:

- The submission makes some use of the data from the pooled trials but relies extensively on data from a registry of Australian patients with CF to estimate the natural history of disease, the rate of exacerbations, and mortality. It was not clear why the control arm of the RCT was not suitable for this purpose; the submission states that the average age at death and the clinical guidelines used were similar in the registry and the trial, which
may not be wholly convincing. While there may be problems with basing the economics on the clinical study results alone, it was not adequately established that the Australian registry was a better fit for Scottish practice than the pooled trials.

- There were some issues with the way the registry data were modelled. The models seemed to have very few explanatory variables. No measures of goodness-of-fit (such as R-squared value), or of predictive power (such as AUROC) were provided.

- The structure of the company’s economic model only considered CF in terms of two types of treatment (with and without inhaled mannitol), exacerbations, waiting for and following a transplant and death (from CF or other cause). The only explicit role for lung function in the model was to determine whether or not the patient was a candidate for a transplant. A more intuitive approach might have been to divide the disease into severity states on the basis of lung function with patients moving between them. The result was that patients’ utility (quality-of-life relative to full health) and NHS cost did not vary as lung function declined. The only exceptions were for exacerbation or transplant; this seems implausible.

- The utility values seem very high: people with CF are assumed to have quality of life that is roughly 90% of normal, which is comparable to an age-sex matched cross-section of the general population who do not have CF. The company suggested that this may be because patients do not appreciate the extent to which their quality of life is limited, but if this is correct then another approach should have been considered. For example, it could have provided an objective description of the symptoms of the disease in a time trade-off survey of members of the public and used the values generated. The high utility value is a source of bias in favour of inhaled mannitol because the extrapolated prediction of added survival is assumed to be in quality of life that is around 90% of normal.

- The comparison made in the economics case submitted does not take account of the fact that hypertonic saline is used in Scotland. While a comparison would certainly be difficult, its omission is problematic since it means SMC does not know the cost-effectiveness of this product compared to a widely-used current treatment.

- The sensitivity analysis did not identify the key drivers of the economics model, apart from the time horizon. A large proportion of the analyses submitted suggested very little impact on the cost per QALY; given the extensive assumptions, the modelling involved and the extrapolation of clinical trial data to a lifetime horizon, this is implausible.

- It was not clear that the group in the RCTs who were not dornase alfa users at the time of the trial matched the population of people who have previously not responded to or not tolerated it, and in whom another trial of dornase alfa would not be considered.

Given these issues, the economic case has not been demonstrated.

Mannitol is an orphan medicine and SMC decision modifiers may apply but in this case there were too many uncertainties in the economic case.
Summary of patient and public involvement

Patient Interest Group Submissions were received from:
- Cystic Fibrosis Trust
- Ivacaftor Patient Interest Group

Additional information: guidelines and protocols

Guidelines published by the Cystic Fibrosis Trust in the UK\(^2\) in 2011 recommend that “Treatment with inhaled dornase alfa or hypertonic saline should be considered as an adjunct to airway clearance.” These guidelines pre-date the availability of inhaled mannitol.

Additional information: comparators

Hypertonic saline (unlicensed).

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhaled mannitol</td>
<td>400mg dry powder inhalation twice daily</td>
<td>6023</td>
</tr>
<tr>
<td>dornase alfa</td>
<td>2500 units (2.5mg) by inhalation of nebulised solution once or twice daily*</td>
<td>6028 to 12,059</td>
</tr>
<tr>
<td>hypertonic saline (7%)</td>
<td>4ml by inhalation of nebulised solution up to twice daily</td>
<td>164 to 328</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs for inhaled mannitol from eVadis on 01 November 2012; costs for hypertonic saline from the BNF, no. 64, September 2012.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 231 in year 1 rising to 245 in year five, with an estimated uptake rate of 20% in year 1 and 55% in year 5. The submitting company has estimated a constant discontinuation rate of 53.01% over the five years. The gross impact on the medicines budget was estimated to be £92k in year 1 and £270k in year 5. As other costs were assumed by the company to be displaced, the net medicines budget impact is expected to be £79k in year 1 and £231k. However, these displaced costs are due to savings in exacerbations which includes hospitalisations costs. These costs are not likely to be cash-releasing; therefore, the net medicines budget impact is likely to be in the region of £92k in year 1 and £270k in year 5.
References

The undernoted references were supplied with the submission. The one shaded in grey is additional to those supplied with the submission.

1. Inhaled mannitol Bronchitol® 40mg inhalation powder, hard capsules, Summary of Product characteristics, last updated 19 June 2012.

This assessment is based on data submitted by the applicant company up to and including 17 December 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.