Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

mannitol 40mg inhalation powder hard capsule (Bronchitol®)

SMC No. (837/13)

Pharmaxis Pharmaceuticals Ltd.

08 November 2013

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

ADVICE: following a resubmission

mannitol (Bronchitol®) is accepted for restricted 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.

SMC restriction: As an add-on to best standard of care in adult patients with CF who are not currently using dornase alfa due to lack of response, intolerance or ineligibility and have rapidly declining lung function and in whom other osmotic agents are considered unsuitable.

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 (FEV_1) over 26 weeks.

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 400mg 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 to15 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]
The patient's initiation dose of 400mg must be used under the supervision and monitoring of an experienced physician or another health care professional appropriately trained and equipped to perform spirometry, monitor oxygen saturation and manage acute bronchospasm including appropriate use of resuscitation equipment.

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 9,000 patients in the UK. There is a high unmet need for new effective treatments for CF. The aim of treatment 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 due to lack of response, intolerance or ineligibility (referred to as *dornase alfa non-users, unsuitable*) and have rapidly declining lung function (≥2% decline in forced expiratory volume in 1 second [FEV_1] % predicted per year, referred to as *fast decliners*) and in whom other osmotic agents are considered unsuitable.

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 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; n=163) and patients not receiving dornase alfa (85mL; 95% CI: 38mL to 131mL; n=132). 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% 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; n=229) and in patients not using dornase alfa (87mL; p=0.12; n=76) 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 to 0.98, p=0.039) and 30% (relative risk 0.70, 95% CI: 0.50 to 0.97, p=0.033), respectively in the mannitol group compared with control.

Table 1. Results of the primary outcome for studies 301 and 302 (ITT population)

	Study 301 (N=295)	**Study 302 (N=305)**
Absolute difference in FEV_1 over 26 weeks (ITT population)	85mL (95% CI 53mL to 117mL)	54mL (95% CI: -2mL to 110mL)*
Absolute difference in FEV_1 over 26 weeks (dornase alfa users)	85mL (95% CI 43mL to 128mL)	43mL (95% CI not reported)*
Absolute difference in FEV_1 over 26 weeks (dornase alfa non-users)	85mL (95% CI 38mL to 131mL)	87mL (95%CI not reported)*

*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.[5]

The company presented results for the sub-group of adult patients which represents the licensed population, and for *dornase alfa non-users, unsuitable* and *fast decliners*. Patients who fulfil the criteria for both of the latter sub-populations represent the proposed positioning. These results have only been published in abstract form.

In a pooled analysis of adult patients from both studies (n=341), the mean absolute difference in FEV_1 for mannitol-treated patients compared with control was 100mL (95% CI: 49mL to 150mL; p<0.001).

In the pooled sub-population of adult *dornase alfa non-users, unsuitable* (n=65), the mean absolute change from baseline in FEV_1 was 181ml for the inhaled mannitol group (n=45) and -12ml for the control group (n=20); difference of 193mL (95%CI: 83mL to 302mL), p=0.007.

In the pooled sub-population of fast decliners (n=85), the difference in absolute FEV_1 over 26 weeks between the inhaled mannitol group and the control group was 124mL (p=0.023).

In adult patients who were *dornase alfa non-users, unsuitable and fast decliners* (n=9 in the inhaled mannitol group and n=4 in the control group), the difference in FEV_1 over 26 weeks was 368mL (p<0.021). This population represents the company's proposed positioning for inhaled mannitol.

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.[1] In both pivotal studies, 7% of patients failed the mannitol tolerance test.

In both studies, the proportion of patients (adults and children) 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 ≥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 Committee for Medicinal Products for Human Use (CHMP) assessment report.[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.[3]

Summary of clinical effectiveness issues

Inhaled mannitol is an orphan medicine that offers an alternative licensed therapy for cystic fibrosis, a life-long, incurable condition. 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 meet all of the following conditions: are not currently using dornase alfa due to lack of response, intolerance or ineligibility, have rapidly declining lung function and in whom other osmotic agents are not appropriate. This represents a very small proportion of the study population and is a narrower population than that covered by the licensed indication, which includes adult patients with CF. This sub-population of adult patients is 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 patients is considered to have a significant unmet medical need, with current therapeutic options for airway clearance being exhausted by the time of adulthood.

The proportion of the pooled study population who were adult *dornase alfa non-users, unsuitable* was 11% (n=65) and adult *fast decliners* represented 14% (n=85). Only 13 patients in the pooled study population met the criteria for inclusion in both sub-groups, which represents the company's proposed positioning. It is acknowledged by the company that the statistical power to detect a treatment difference in these small patient groups is substantially reduced.

The company submitted the results of post-hoc pooled sub-group analyses in adults aged ≥18 years who were *dornase alfa non-users, unsuitable* and *fast decliners*; 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 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 FEV_1 measured at 26 weeks and the treatment effect was maintained in both studies up to 52 weeks in open-label extension studies.

There was no significant difference in the rate of protocol-defined pulmonary exacerbations in either study, although the studies were not powered to show a difference in this outcome. There was a reduction in the incidence of PDPEs of approximately 25% in study 301 and 15% in study 302 although the EMA noted the treatment period was not long enough to allow adequate assessment of this outcome.[3]

The proposed positioning would offer a treatment option for patients with rapidly declining lung function who are not suitable for treatment with dornase alfa and in whom other mucolytic agents are not appropriate, where there is an unmet need for an effective treatment. This is likely to represent a minority of adult patients with CF in Scotland. The company has proposed

that patients should be assessed for any improvement in lung function after six weeks to evaluate the appropriateness of continuing treatment and experts agreed that six weeks was a reasonable time in which to assess response.

Inhaled mannitol 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 cost-utility analysis using a patient simulation model of adding inhaled mannitol to best supportive care (BSC) for adult patients with CF; the proposed positioning was for use in people who are not currently using dornase alfa due to lack of response, intolerance or ineligibility, have rapidly declining lung function and in whom other osmotic agents are not appropriate.

Despite this proposed positioning, the submitting company performed base case evaluations using patient level data from the pooled analysis of the mannitol studies in two alternative sub-groups, consisting of patients who are dornase alfa non-users (n=134), and a separate sub-group of patients who have rapidly declining lung function (fast decliners) which includes users of dornase alfa (n=85). A scenario analysis has been performed for a sub-group of patients who are fast decliners and dornase alfa non-users; these are stated to most closely reflect the patients for the proposed positioning. This was based on the fast decliner analysis with the only change consisting of the exclusion of the costs of dornase alfa use (as a proxy for non-use of dornase alfa). A scenario analysis which includes dornase alfa non-users, unsuitables (n=65) was also provided.

The model adopted a lifetime horizon and consisted of patients starting in a CF health state, with risks of pulmonary exacerbations (requiring hospitalisation), and if FEV_1 declined to below 30% of predicted, a 0.17 probability of requiring a lung transplant based on data from the UK CF Trust Registry. Mortality risk was from a number of main sources: decline in FEV_1, exacerbations plus having Burkholderia capacia complex (Bcc) infection, and post lung transplant mortality. Regression analysis has been used to estimate the mannitol treatment effect on change in FEV_1 % at 26 weeks for each sub-group, and the natural history rate of decline in lung function was extrapolated beyond the trial using regression analysis based on an Australian longitudinal observational dataset in CF adult patients aged 18-47 years. The relative risk of exacerbation was derived from trial data, and the annual probability of an exacerbation was derived from the Australian dataset. Survival analysis was performed using a Cox Proportional Hazards model to estimate mortality associated with decline in FEV_1. The probability of transplant related mortality was derived from published 10 year UK lung transplant survival estimates. In terms of extrapolation of outcomes, as long as the patient remains on treatment, the benefit of mannitol over BSC is maintained.

Data on quality of life were taken from several sources. The Health Utilities Index-2 measure was used in the clinical trials with the baseline value used for each sub-group to provide an estimate of the utility associated with the CF health state. The utility decrement associated with exacerbations (-0.25 adjusted for time spent with an exacerbation estimated to be 14 days) was

derived from a recently published study in UK CF patients, and pre- and post-transplant utility data from previously published research.

The cost of mannitol was based on a dose of 800mg per day, and the cost of an initiation dose assessment test was included. For resource use, data were taken from the pooled clinical studies and included a full range of hospital and community care costs for CF. The costs of lung transplant and 15 year follow-up costs were based on NHS reference costs and a published study. Costs of concomitant medication (predominantly antibiotics) were also included. In the fast decliners sub-group, the use and cost of dornase alfa was included. The economic analysis also applied a stopping rule (defined as no increase in FEV_1 or FEV_1 % predicted), whereby treatment with mannitol would be discontinued if there is no response at 6 weeks and patients switched to BSC. Responding patients discontinued treatment at the rate of drop-outs measured in the pooled trials.

The company's base case estimate for the cost-effectiveness of inhaled mannitol in the dornase alfa non-user sub-group was an incremental cost-effectiveness ratio (ICER) of £20,814 per quality-adjusted life-year (QALY) gained, based on an incremental cost of £10,617, incremental life years gained and QALYs gained of 0.54 and 0.51 respectively. In the fast decliners sub-group, the ICER was £25,935 per QALY gained based on an incremental cost of £23,549, incremental life years gained and QALYs gained of 0.73 and 0.91 respectively. Sensitivity analysis around mortality variables did not show high sensitivity to varying parameters such as the FEV_1 hazard ratio. Shortening the time horizon to 5 years increased the ICER in the dornase alfa sub-group to £39.4k per QALY, but for the fast decliner sub-group led to mannitol dominating BSC. A scenario analysis in the group defined as fast decliner and dornase alfa non-user produced an estimated ICER of £20,716 per QALY gained. As the only difference from the fast decliner model was the exclusion of dornase alfa costs, the outcomes were the same but lower incremental costs were estimated (£18,810) due to higher use and costs of dornase alfa in the mannitol group of fast decliners.

There are several issues and concerns with the analyses performed:

- The base case analyses are not directly relevant for the proposed product positioning, being broader in coverage. The company recognised this but stated that their approach is pragmatic. By producing cost-effectiveness results in broader sub-groups that are aligned to the sub-group of interest, the company proposed that it is possible to infer similar cost-effectiveness in the very small target patient population (n=13), for which there is a shortage of clinical data from the studies. The company subsequently provided an analysis based on the target patient population which indicated the ICER in this sub-group was £20,840 per QALY gained. However, this analysis is based on clinical data from a very small sub-group of patients.
- The scenario analysis for the fast decliner, dornase alfa unsuitable, population that is closest to the target population for the proposed positioning could result in unreliable ICER estimates. The analysis is based on fast decliners outcomes only so effectiveness in patients who are dornase alfa non-users/unsuitable is not accounted for. The use and costs of dornase alfa in the fast decliner analysis is higher in the mannitol arm than the BSC arm; excluding the costs of this use but not adjusting for possible additional effectiveness could bias the ICER estimate.
- There were a number of concerns regarding the lack of transparency about the drivers of the mortality benefits and QALY gains estimated for mannitol. The company provided additional graphs that appear to show significant mortality benefits for mannitol associated with declining FEV_1 in the dornase alfa non-user sub-group and from a

reduced need for lung transplant and associated mortality in the fast decliner sub-group. However, they also showed worse survival outcomes compared to BSC alone as the result of CF related mortality and background mortality (which is not clearly defined) in both sub-groups.

- There are also concerns over the modelling approach that allows lung function to decline and impact on risk of CF mortality, but not to impact on health related quality of life over time (maintained at a high level of around 0.9) or on resource use. As survival is improved with mannitol in the model, retaining a high utility level could benefit the treatment in the additional survival years. In a scenario analysis applying a linear association between reduction in utility and lung function decline, the ICER increased to above £30k per QALY for the fast decliner group but improved for the dornase alfa non-user group.

SMC considered the likely range of cost-effectiveness ratios and the uncertainties with the analysis. Although there were some limitations with the economic analysis, the economic case was considered demonstrated when the orphan status of the medicine and the small patient group who would be eligible to receive mannitol were considered.

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

Best supportive care. Dornase alfa and hypertonic saline (unlicensed) are alternative treatments for CF, but would not be considered comparators in the context of the company's proposed positioning.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
inhaled mannitol	**400mg dry powder inhalation twice daily**	**6,023**
dornase alfa	2,500 units (2.5mg) by inhalation of nebulised solution once or twice daily*	6,024 to 12,048
hypertonic saline (7%)	4mL by inhalation of nebulised solution up to twice daily	164 to 328

Doses are for general comparison and do not imply therapeutic equivalence. All costs from British National Formulary (BNF) 65 on 04 September 2013; * The BNF states that patients over 21 years may benefit from twice daily dosing.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 35 in year 1 rising to 37 in year 5, assuming an uptake rate of 100% in these patients. The submitting company has estimated a constant discontinuation rate of 47.2% over the five years, meaning 19 patients treated in year 1, and 20 in year 5. The gross impact on the medicines budget was assumed to be £151k in year 1 and £160k in year 5. As other medicines costs associated with exacerbations were assumed by the company to be displaced, the net medicines budget impact is expected to be £135k in year 1 and £143k 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 12 February 2013.
2. Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK, Second edition, December 2011. http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/
3. European Medicines Agency. CHMP Assessment Report for inhaled mannitol (Bronchitol®).16 February 2012. EMA/CHMP/121817/2012 www.ema.europa.eu
4. Bilton D, Robinson D, Cooper CG et al. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. European Respiratory Journal 2011; 38: 1071-1080.
5. Aitken ML, Bellon G, De Boeck K. et al. Long-term inhaled dry powder mannitol in cystic fibrosis: An International Randomised Study. Am J Resp Crit Care Med 2012; 185; 6: 645-652.

This assessment is based on data submitted by the applicant company up to and including 11 October 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.