Cost-effectiveness of mannitol dry powder for inhalation (Bronchitol®) for the treatment of adult patients with cystic fibrosis as an add-on therapy to best standard of care.

The NCPE has issued a recommendation regarding the cost-effectiveness of mannitol dry powder for inhalation (Bronchitol®) for the treatment of adult patients with cystic fibrosis (CF) as an add-on therapy to best standard of care (BSC). The NCPE does not recommend reimbursement of Bronchitol®.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the company's (Pharmaxis) economic dossier on the cost-effectiveness of mannitol dry powder for inhalation (Bronchitol®) for this indication. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **August 2014**

In March 2014 Pharmaxis submitted a clinical and economic dossier on the cost-effectiveness of mannitol dry powder for inhalation (Bronchitol®) for the treatment of adult patients with cystic fibrosis (CF) as an add-on therapy to best supportive care (BSC). Bronchitol® is an inhaled hyperosmotic medicinal product which aids in mucus clearance from the lungs. Bronchitol® is administered at a dose of 400mg (10 x 40mg capsules) twice daily via inhaler.

1. Clinical effectiveness of Bronchitol®

- The Bronchitol® licence allows for use of the drug as an add-on to BSC in adults. The comparator included by the company (Pharmaxis) in the original pharmacoeconomic evaluation was BSC alone. The NCPE review team considered that hyperosmotic therapy (hypertonic saline) and the commonly used rhDNase (Pulmozyme®) should also be included as comparators. In the model patients were considered to be ineligible or have not responded to hypertonic saline and that Bronchitol® would be used in addition to rhDNase. Therefore neither of hypertonic saline or rhDNase was included as comparators.
- The clinical efficacy was based on two 26-week, double blind, randomised controlled trials of Bronchitol® 400mg twice daily compared to a control group receiving Bronchitol® 50mg twice daily (considered sub-therapeutic) in patients aged over 6 years of age (DPM-CF-301 and DPM-CF-302). The licence is for adults aged over 18 years, therefore the clinical efficacy was based on a subgroup analysis including only the adult patients from the trials. The trials were considered sufficiently similar to directly pool the data. The pooled adult data showed a mean absolute change in FEV_1 of +92.9ml with Bronchitol® 400mg compared to -7.1ml with control, a difference of 100ml ($p<0.001$). A more clinically informative measure of lung function is absolute change in FEV_1 % predicted. An improvement of 2.39% was seen in the Bronchitol® patients compared with a 0.05% deterioration in the control group, a difference of 2.43% ($p<0.001$). Additionally a 24.2% reduction was observed in the incidence of exacerbations with the use of Bronchitol® compared to control. However, the relative risk of developing an exacerbation was not statistically significant 0.76 (95% CI: 0.51, 1.13). The NCPE review team had concerns regarding these results due to the use of sub-population data from the trials, the large number of drop-outs seen in the

trials, the non-statistically significant difference in exacerbations experienced and the clinical significance of the small effects on FEV_1 observed.

- The clinical efficacy data underpinning the company's economic model used the clinical trial data to inform a linear regression analysis for absolute change in FEV_1 % predicted over 26-weeks. This analysis incorporated: treatment group, BMI at baseline, FEV_1 % predicted at baseline, number of exacerbations and being a responder to Bronchitol® treatment i.e. showing any improvement in lung function.

2. Safety of Bronchitol®

- The most commonly reported adverse event in the clinical trials was 'condition aggravated'. The most commonly reported adverse event considered as possibly related to study medication was cough. Other treatment-related adverse events were decreased appetite, headache, haemoptysis, bronchospasm, condition aggravated, pharyngolaryngeal pain, productive cough and chest discomfort. From a clinical point of view, haemoptysis is the most relevant adverse event observed with Bronchitol® treatment due to its potential severity, with 5.8% of adult Bronchitol® and 3.0% of adult control patients experiencing symptoms.

3. Cost effectiveness of Bronchitol®

Methods

- A cost-utility analysis comparing Bronchitol® with BSC was submitted by Pharmaxis. The NCPE review team questioned the exclusion of hypertonic saline and pulmozyme® as comparators in the model. Health benefits were measured in quality-adjusted life years (QALYs) and disutilities associated with exacerbations, requiring a lung transplant and following a lung transplant were included. Costs included drug acquisition, health state costs and costs associated with an exacerbation and lung transplant, from the healthcare payer's perspective.
- A multi-state patient-level micro-simulation Markov model was used, which simulates the progression of each individual patient over a lifetime horizon, updating

patient characteristics such as lung function, age and body mass index (BMI) over time.

- The model was constructed around three regression analyses. The first was derived from the clinical trial dataset estimating FEV_1 % predicted at 26 weeks and a second reflecting a natural history decline in FEV_1 % predicted derived from an Australian longitudinal patient-level dataset (Biogrid). A third regression model (also based on the Biogrid dataset) was used to incorporate CF-related mortality as patients transition through the model. The NCPE review team questioned the generalisability of using Australian data for an Irish population.
- The model included a 'responder' rule under which patients whose condition does not respond to Bronchitol® within 6 weeks cease treatment and switch to BSC. This was included as the company proposed limiting use to those that are inadequately controlled by BSC and have trialled and failed use of hypertonic saline and who continue to respond to treatment. The NCPE questioned the feasibility of restricting treatment to this patient sub-population in clinical practice. A scenario analysis was presented by the company with removal of this 'responder' rule which the NCPE review team considers is more appropriate.

Results

- Total lifetime costs and QALYs of Bronchitol® treated patients were estimated at €606,399 and 13.10 respectively, corresponding to an additional €18,370 and 0.54 QALYs compared with BSC. This resulted in an incremental cost/QALY compared with BSC of €33,772.
- The scenario analysis with removal of the 'responder' rule estimated an additional €26,243 and 0.67 QALYs with Bronchitol® compared with BSC. This resulted in an incremental cost/QALY compared with BSC of €39,243.
- Further sensitivity analyses demonstrated that the model is most sensitive to the relative risk of experiencing an exacerbation for patients who are responders to Bronchitol® and the annual drop-out rate for Bronchitol® responders. Varying the other model parameters had little impact on the incremental cost effectiveness with none reaching a willingness-to-pay threshold of €45,000/QALY.
- The probabilistic sensitivity analysis indicated that the probability of Bronchitol® being cost-effective at €45,000/QALY was 74%.

4. Budget impact of Bronchitol®

The projected cumulative gross budget impact (incorporating the licenced indication i.e. all adults with CF), based on company estimates of market share, is €5.1 million over the next 5 years.

5. Conclusion

Bronchitol® is licenced for the treatment of CF in adults aged 18 years and above as an add-on therapy to BSC. Pharmaxis propose that this population be limited to adult CF patients that are inadequately controlled by their existing treatment and for whom other osmotic agents are not considered appropriate and who continue to respond to treatment. Therefore the company submitted a dossier based on this patient sub-population for which the budget impact is lower.

The NCPE do not consider that the evidence used to support the cost effectiveness of Bronchitol® in the general CF population to be robust and that the case for cost-effectiveness has not been proven.