Cost-effectiveness of Ataluren (Transarna™) for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophy gene in ambulatory patients aged 5 years and older

The NCPE has issued a recommendation regarding the cost-effectiveness of ataluren (Translarna™). Following NCPE assessment of the applicant's submission, ataluren (Translarna™) is not considered cost-effective for the treatment of duchenne muscular dystrophy resulting from a nonsense mutation in ambulatory patients aged 5 years and older and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (PTC Therapeutics International Limited) economic dossier on the cost effectiveness of ataluren (Translarna™). 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, which 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 which 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 a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **April 2016**

Summary

In October 2015, PTC Therapeutics International Limited submitted a dossier examining the cost effectiveness of ataluren for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (nmDMD), in ambulatory patients aged 5 years and older. Final data submitted by the Applicant was received in January 2016.

The recommended dose is 40mg/kg body weight. Dosing frequency is three times a day (10mg/kg in the morning, 10mg/kg at midday and 20mg/kg in the evening). The anticipated use of ataluren includes discontinuation once boys become non-ambulatory, as efficacy has not been demonstrated in non-ambulatory patients. It is formulated in granules for oral suspension, available as 125mg, 250mg and 1000mg sachets.

There is no existing therapy for nmDMD that treats the underlying cause of the disease. Currently, the disease is managed in a multidisciplinary care setting including glucocorticoids, physical therapy, and psychosocial care as well as supporting medical devices. Ataluren can be given in addition to current best supportive care (BSC). The comparator for the cost effectiveness analysis is BSC alone.

1. **Comparative effectiveness of ataluren**

Study 007, a placebo controlled, randomised, multi-centred, double blind phase 2 trial, provided evidence of comparative effectiveness of ataluren compared with placebo. 174 patients were randomly assigned to receive either 40mg/kg/day of ataluren (n=57), 80mg/kg/day of ataluren (n=60) or placebo (n=57) for 48 weeks. Patients were stratified by baseline 6MWD (distance walked over 6 minutes), age and corticosteroid use.

The primary endpoint was the change in decline of 6MWD (distance walked over 6 minutes) at 48 weeks. Secondary outcomes included time function tests (to assess changes in proximal muscle function), step activity monitoring (to assess changes in the activity in the community) and myometry (to assess changes in force exerted during knee or elbow flexion and extension and shoulder abduction). Self reported outcomes included the paediatric Quality of Life Inventory (PedsQL), treatment satisfaction questionnaire for medication and changes in wheelchair use and number of accidental falls. Secondary outcomes also

included measures to assess the cognitive and cardiac function of the patients as well as pharmacodynamic information.

The mean age of patients in the study was 8.5 years with a mean body height of 125cm and a mean weight of 31kg. Mean baseline 6MWD was 356 metres. Age at diagnosis varied widely from 0 to 10 years, as did age at recruitment (5 to 20 years).

Results presented here are based on a corrected intention to treat (cITT) population, which replaced baseline physical function measures with measures obtained at screening for two patients, who had suffered an injury, which was later resolved.

No effect was observed for the higher 80mg/kg/day dose. The applicant explained this with a bell-shaped concentration-response relationship shown in nonclinical in vitro experiments.

The objective of the study was to show a mean difference in decline of 6MWD of 30 metres at 48 weeks. 30 metres has previously been shown to be the minimal clinically important difference (McDonald 2013).

The 40mg/kg/day dose of ataluren achieved a mean difference of 31.7m (95%CI: 5.1m, 58.3m). A hazard ratio of 0.51 was estimated for the proportion of patients with a 10% of worsening in 6MWD for patients with ataluren compared to placebo.

A trend towards better outcome was observed in the timed function tests.

Outcomes in accidental falls were considered important by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA); however, since baseline values varied between the two groups, outcomes were not deemed indicative of a true effect of ataluren.

The CHMP considered the definition of wheelchair use as a count of days in which wheelchairs were used as not appropriate to capture the necessary variability of the outcome.

In step activity monitoring a trend was observed to spend less time in no activity with ataluren; however, results were considered inconclusive due to the small difference.

No effect on muscle strength as measured using myometry could be observed, which might be due to the short time horizon of the study.

The applicant presented a post-hoc subgroup analysis of patients in the decline phase (n=63) (patients older than 7, treated with corticosteroids, baseline 6MWD >= 150m and <80% predicted 6MWD). A mean difference of 50m in mean 6MWD was observed in favour for ataluren. Similar clinically meaningful improvements were observed in secondary

outcomes including time function tests. This indicates that in the short duration of the trial, patients in the decline phase showed a greater benefit from ataluren compared to the full population. The applicant considers that ataluren should be given before the decline phase to maximise efficacy.

2. Safety of ataluren

The applicant provided evidence of the safety of ataluren based on combined data from several studies (007, 004, 007e, 004e, 016 and 019). Ataluren was generally well tolerated by patients with nmDMD. Most common adverse events (reported in >20% of patients) in the combined safety profile included headache (41%), diarrhoea (27%), nasopharyngitis (26%), cough (25%), upper abdominal pain (22%), pyrexia (22%), fall (21%) and upper respiratory tract infection (21%). These are common adverse events of paediatric illnesses or DMD complications. Serious adverse events were reported in 3.5% of patients treated with ataluren compared with 5.3% of patients in the placebo arm (study 007). None were considered by the investigator to be related to ataluren.

Phase 1 studies showed signals that ataluren might elevate liver enzymes, serum cholesterol and triglycerides. Cases of hepatic toxicity and increased levels of cholesterol and triglyceride were also observed in study 007. While hepatic toxicity was reversible when ataluren was stopped, this may be of less relevance since ataluren is indicated for continuous use. Hepatotoxicity, and increases in cholesterol and triglyceride levels are considered an important safety concern by the CHMP, and need to be managed.

3. Cost effectiveness of ataluren

Methods

- A Markov model estimated the costs and health benefits over the lifetime of the cohort. Patients progress from an ambulatory health state to non-ambulatory health states; where they can develop scoliosis, require assisted ventilation or both. Patients die from non-DMD causes in the ambulatory states and from DMD and non-DMD causes once ambulation is lost.
- The mean age of the cohort entering the model is 8.5 years in line with the cohort in the clinical trial. However, it is likely that patients will be treated from age 5 as per the licensed indication. While patients are unlikely to show a significant benefit in

this earlier phase, a considerable cost is accumulated during these 3.5 years. The review group have added the drug costs accumulated during this time to the costs of ataluren in their preferred scenario.

- Parametric curves fitted to Kaplan Meier plots obtained from the literature inform the transition between health states. Ricotti et al. (2013), a prospective, longitudinal study in the UK, provides evidence to inform time to loss of ambulation in the BSC arm. Humbertclaude et al. (2012) analysed the French dystrophinopathy database and informs the development of scoliosis and the need for ventilation assistance. Due to a flattening of the Kaplan Meier observed in the study, the applicant assumes that no scoliosis will develop after the age of 17. The analysis of Van den Bergen et al. (2014) of Dutch patients informs DMD related death in the BSC arm.
- The effect of ataluren is modelled using the effects on 6MWD observed over 48 weeks.
    - The manufacturer assumes a linear relationship of the treatment effect with time and thereby estimates a delay in loss of ambulation of 8.1 years.
    - The assumption of no development of scoliosis after the age of 17 results in an implicit significant reduction in scoliosis in the ataluren arm, since patients lose ambulation at a median age of ~21 years.
    - A survival benefit is implicit in the assumption of prolonged ambulation and associated reduction in DMD-related mortality. The applicant assumes an additional benefit on overall survival with ataluren applied through a HR. There is no trial data supporting this benefit.
    - The applicant further assumes a benefit on quality of life of 0.13 once ambulation is lost. There is no data supporting this assumption.
- Health state costs and utilities are taken from Landfeldt et al. However, this study distinguishes between early and late ambulatory as well as early and late non-ambulatory health states, which do not represent the health states in the model. The applicant applied the early ambulatory costs and utilities to the ambulatory health state. The applicant applied the utility estimated for early non-ambulatory health state to the non-ambulatory health state in the ataluren arm, and the late non-ambulatory health state utility to the non-ambulatory health state in the BSC arm. No utility reduction for ventilation assistance is applied; a reduction of 0.2 is applied

for scoliosis (no supporting data is provided). Late non-ambulatory costs estimated by Landfeldt et al. are applied to all non-ambulatory health states in the model. Separate once off costs are applied for scoliosis surgery and ventilation equipment. NCPE review group concerns include:

- health states in the publication used to populate the model do not represent the health states used in the economic model. Differential utility values are applied to the same health states for ataluren and BSC
- It is unclear in the Landfeldt study whether scoliosis costs and ventilation equipment are already accounted for.

Results

- The basecase presented by the applicant estimates an incremental cost of €5,303,434 for the gain of 5.284 QALYs or 1.268 life years. This results in an incremental cost effectiveness ratio (ICER) of €1,003,637/QALY.
- Based on the NCPE preferred set of assumptions, the analysis estimates an incremental cost of €6,820,784 for the gain of 2.928 QALYs or 0.710 life years, yielding an ICER of **€2,329,281/QALY**.
- NCPE preferred assumptions include: consistent health state utility values across the economic model, application of a caregiver disutility as reported in the source publication, limitation of the survival benefit of ataluren to that associated with delayed loss of ambulation, application of treatment costs from 5-8.5 years of age and for 6 months after loss of ambulation, removal of generic pricing assumption post patent expiry as well as assuming reimbursement under the high tech drug scheme.

Sensitivity analysis

- The initial submission did not include a probabilistic sensitivity analysis. Upon request, the applicant submitted results of a probabilistic analysis, however, the model was not submitted for review. The review group feel that the uncertainty in the effects of ataluren (given the short duration of the trial and the surrogate outcome measure) is not captured appropriately. Nevertheless, due to the high

cost of ataluren, even with underestimated uncertainty, the probability of cost effectiveness at a threshold of €45,000/QALY, €100,000/QALY or €500,000/QALY is equal to 0%.

- A number of scenarios show that under none of the assumptions, the ICER comes close to the current willingness to pay threshold.
- The applicant presented results of a one-way sensitivity analysis. The ICER did not fall below ~€850,000/QALY for any of the variables varied.

4. Budget impact

The proposed ex-manufacturer price of ataluren is €3,072 per 30-sachet pack. The annual ex-manufacturer cost for a ten-year old of average weight is €411,136. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €5.8 million (increasing from €0.6 million in year 1 to €1.8 million in year 5). Long-term budget impact projections, taking account of increasing body weight, increase to approximately €9.4 million over five years.

5. Conclusion

Following NCPE assessment of the company submission, ataluren (Translarna®) is not considered cost-effective for the treatment of nmDMD and is therefore not recommended for reimbursement.