Cost-effectiveness of cerliponase alfa (Brineura®) for the treatment of patients with CLN2 disease

The NCPE has issued a recommendation regarding the cost-effectiveness of cerliponase alfa (Brineura®). Following assessment of the applicant's submission, the NCPE recommends that cerliponase alfa (Brineura®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Biomarin) economic dossier on the cost effectiveness of cerliponase alfa (Brineura®). 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 **March 2019**

Summary

In August 2018, BioMarin submitted a dossier examining the clinical, safety and economic evidence in support of an appraisal of the cost-effectiveness and budget impact of cerliponase alfa (Brineura ®) for the treatment of patients with Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disease. CLN2 disease is a rare, paediatric-onset neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency as a consequence of loss-of-function mutation in the CLN 2 gene. CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), which may also be collectively referred to as Batten disease. All these disorders affect the nervous system and typically cause worsening problems with vision, movement, and thinking ability. The signs and symptoms of CLN2 disease typically begin between ages 2 and 4. The initial features usually include recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects motor skills, such as sitting and walking, and speech development. This condition also causes the loss of previously acquired skills (developmental regression), intellectual disability that gradually gets worse, and behavioural problems. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens. Treatment is currently limited to symptomatic and supportive care. BioMarin are seeking reimbursement for cerliponase alfa in the hospital setting. As there are no other licensed treatment options available for CLN2 disease, it is anticipated that cerliponase alfa will be used as first-line therapy within it's marketing authorisation.

1. Comparative effectiveness of cerliponase alfa

The primary sources of clinical efficacy estimates are provided by Study 190-201 and Study 190-202. Study 190-201 (n=23) provided clinical evidence for the cerliponase alfa arm of the economic evaluation, for the first 48 weeks of treatment. The longer-term extension study, Study 190-202, provided additional longer term clinical evidence. Study 190-202 followed the patients in Study 190-201 with a reporting period at 96 weeks. Longer term observations had been made post week 96 however it was difficult to draw any definitive conclusions on the efficacy of cerliponase alfa beyond this timepoint.

Both Study 190-201 and Study 190-202 were single-arm, open-label studies. The applicant stated that it was not considered ethically acceptable to undertake placebo-controlled trials due to the requirement for intracerebroventricular (ICV) surgery and due to the rapid progression of the disease. Therefore, the clinical evidence for standard care was derived from treatment naïve patients with CLN2 disease in Study 190-901, which was a natural history study based on a retrospective database review. The patients in Study 190-901 were from the DEM-CHILD cohort, which has participating sites in both Germany and Italy.

A matching analysis was undertaken, where patients from Study 190-201/202 were matched to a patient in the Study 190-901 based on a 1:1 matching algorithm. Matching was undertaken based on the patients' CLN2 clinical rating scale score and age within 12 months. A total of 22 matched comparisons were made (from the initial n=23).

The primary responder analysis showed a statistically significantly higher proportion of responders with a decrease in the rate of disease progression (rate <2/48 weeks) in the cerliponase alfa arm (91%) as measured by the adapted CLN 2 scale compared to the historical controls (45%). The estimated difference in response rates was 46% (p=0.0028). Results from pre-specified sensitivity analyses supported the findings from the primary analysis of a statistically significant difference in response between treated patients and natural history patients (p=0.0001 to <0.0001).

2. Safety of cerliponase alfa

From the pivotal trials (190-201 and 190-202) all subjects experienced at least one treatment-emergent AE. Twenty three (96%) subjects experienced at least one drug related adverse event (AE) and 19 (79%) subjects experienced at least one serious adverse event (SAE). Drug related SAEs occurred in 8 (13%) subjects. The most common AEs were pyrexia (71%), seizure (58%), vomiting (58%) and upper respiratory tract infection (50%). Other common events included epilepsy and generalized tonic-clonic seizures (46% each), rhinitis (42%) and hypersensitivity and nasopharyngitis (38% each). It should be noted that the clinical safety database derived from studies 201/202 is considered limited. No clinical data is available in patients below 2 years of age as well as in subjects with advanced CLN2

disease and limited experience is available in subjects above 8 years of age. Causality assessment of reported AEs is difficult as the clinical studies were uncontrolled and several AEs may have different causes including active substance, device and underlying disease. The CHMP have requested the applicant to monitor the long term safety of cerliponase alfa for the treatment of CLN2 disease.

3. Cost effectiveness of cerliponase alfa

Methods

A de-novo cost-utility analysis comparing cerliponase alfa with SoC was undertaken. A multi-state Markov model structure was implemented for the economic analysis. The Health Service Executive (HSE) perspective and a lifetime time horizon (equating to 95 years) were used. This time horizon is sufficiently long to capture the costs and benefits over CLN2 patients' lifetimes. However, the Review Group (RG) were concerned with the data and assumptions used in the model to populate this lifetime horizon. The cycle length chosen for the model was 2 weeks. The RG considered that the cycle length used is relatively short.

The Markov model consisted of 10 health states, which were based on the CLN2 clinical rating score and other clinical characteristics. Health states 1-7 were defined by the CLN2 Clinical Rating Scale, which ranges from a score of 6 (for least severe) to a score of 0 (for most severe). Health state 8 was defined as score of 0 on the CLN2 Clinical Rating Scale with the addition of complete vision loss for patients in that health state. Health state 9 is the same as health state 8, with the additional requirement for palliative care. Health state 10 was the absorbing death state. The model structure was generally appropriate to the disease process of CLN2 disease, although the RG did have some concerns. The main clinical outcome represented in the model is the decline in CLN2 clinical rating scale scores in patients. The early part of the model reflects current knowledge of the clinical pathway of the patients, adequately modelling the changes in their CLN2 rating scale scores. However,

given the lack of long-term outcome of this disease when a treatment is available, it is not possible to ascertain if the model reflects the long-term outcomes of these patients.

The baseline distribution of patients, that is, where patients enter the economic model, was estimated by the applicant and it was assumed that the expected population in Ireland would start in the Health State 1 (ML score 6). This is a strong assumption, assuming that all patients will be diagnosed in Ireland before their motor and language function is affected by CLN2 disease. Therefore, the RG considered it more prudent to assume the starting population would be that of the trial population and undertook a scenario analysis using the baseline distribution from the trials.

Cerliponase alfa alters the disease course of CLN2 in the model, by delaying disease progression, i.e. the transition to more severe health states. Patient level data from Study 190-201/202, along with matched patients from Study 190-901 informed the transition probabilities for the cerliponase alfa arm and the no treatment arm. Due to the small patient numbers in the trial, some health states were combined to calculate the transition probabilities. The mean time taken for transition between Health states 7-8 and health states 8-9 was assumed to be 52 weeks for both arms in the model.

Although the model structure is broadly appropriate to capture disease progression of CLN2, at least for the initial treatment phase, it is important to note that the data used to inform the transition probabilities was limited to small trials with short time horizons (especially when compared with the time horizon of the model); this will result in very small numbers informing the transition probabilities, which increases the uncertainty of these estimates. In addition, some strong assumptions around the long-term treatment effectiveness of cerliponase alfa were incorporated into the model.

The RG considered that the applicant's assumption that all cerliponase alfa patients achieved disease stabilisation by week 96 to be optimistic and subject to considerable uncertainty. The RG presented a scenario which relaxed the stabilisation assumption to give an indication of the direction of change in the ICER, should the stabilisation assumptions not materialise in future patients.

Standard of care (SoC) is considered to be the only comparator of interest in this submission, given that there are currently no other licensed treatment options for patients with CLN2 disease. All relevant costs were included in the model, for example, drug acquisition and administration costs, healthcare professional costs and hospital costs; psychiatric support costs; residential care costs; electrocardiogram costs; and costs associated with progressive symptoms/seizures/vision loss. Healthcare resource use data were derived from Study 190-201/202 and published literature.

Results

Applicant base case

- In the deterministic analysis, cerliponase alfa was associated with 14.71 greater QALYs at a greater cost of €11,314,065, resulting in an ICER of €769,332/QALY.
- In the probabilistic analysis, cerliponase alfa was associated with 30.42 greater QALYs at a greater cost of €24,562,179, resulting in an ICER of €807,458/QALY.

Although the ICER is relatively unchanged between the deterministic and probabilistic results, the total costs and QALYs for cerliponase alfa change quite dramatically. This highlights the uncertainty surrounding the results.

NCPE preferred base case

The NCPE preferred base case analysis includes the following assumptions:

- Disutilities not relevant to the HSE perspective have been removed;
- The baseline distribution of patients across the health states was based on that observed in the 190-201/202 study;
- The disease stabilisation of all cerliponase alfa patients at Week 96 assumption has been relaxed.

Cerliponase alfa was associated with 4.96 greater QALYs at a greater cost of €6,699,998, resulting in an ICER of €1,349,601/QALY for the NCPE preferred base case.

4. Budget impact of cerliponase alfa

The price to wholesaler for the 2x150mg pack is €20,384.62. The annual cost, per patient, to the HSE is €622,750.18.

Based on prevalence figures from published literature, it is estimated that there will be zero eligible patients in Year 1, one eligible patient in Years 2 and 3 and two eligible patients in Year 4 and 5. The cumulative five year gross budget impact for cerliponase alfa is estimated to be €5,265,437. This figure includes the annual cost associated with the replacement of the ICV device. As there are currently no treatments indicated for CLN2 disease, there are no expected potential drug cost-offsets. Therefore, the net budget impact is considered to be the same as the gross budget impact.

When the budget impact analysis takes account of the costs associated with certain health states, progressive symptoms and chronic seizures being offset, the cumulative five year budget impact for cerliponase alfa reduces to €5,159,376.

5. Patient submissions

No patient submissions were received.

6. Conclusion

Within the trial data, treatment with cerliponase alfa over 48 weeks demonstrated a significant effect on disease progression, as measured by the response rate and rate of decline in the ML score. Sustained treatment effect was observed up to 96 weeks. However, the applicant's data does not support a case for the longer term benefits of cerliponase alfa outside the clinical trial period (i.e. >96 weeks).

Following assessment of the applicant's submission, the NCPE recommends that cerliponase alfa (Brineura®) not be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.