Urgent Clinical Commissioning Policy Statement: Cerliponase alfa for neuronal ceroid lipofuscinosis Type 2 (CLN2) in children

NHS England Reference: 170017/P
1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England’s values. Throughout the development of this policy statement, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

In the interests of delivering an urgent commissioning position, a rapid initial equality impact assessment has been carried out and a full equality health impact assessment will be undertaken when a clinical commissioning policy is published to replace this document.

2 Background

Neuronal ceroid lipofuscinoses are a genetically heterogeneous group of inherited neurodegenerative lysosomal storage disorders. The different neuronal ceroid lipofuscinoses are distinguished by the genetic origin, ultrastructural composition of the lysosomal storage material, clinical symptoms, age at disease onset and course of disease.

Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disorder is a rare, paediatric-onset neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency as a consequence of loss-of-function mutation in the CLN2 gene.

Patients with CLN2 disease typically present with slowing of development and psychomotor regression, usually in the second or third year of life. The diagnosis is on average confirmed at 4 years of age. Epilepsy typically develops early, between 2 and 4 years of age, usually presents with variable seizure types and is often refractory to treatment. Patients further develop ataxia, myoclonus (muscle spasms), impaired speech and cognition as well as developmental regression. The visual, cognitive and motor skills decline rapidly. The general decay of psychomotor function is rapid and uniform between the third and fourth birthday. Some children become extremely irritable and distressed. Limb spasticity may become prominent with weakness of muscles in the trunk and loss of head control.

In general, patients lose vision, are wheelchair-bound and require gastrostomy feeding at approximately 6 years of age. They subsequently enter a vegetative state with death occurring between 10 and 16 years of age.
Cerliponase alfa is a recombinant form of the TPP enzyme which is missing or inactive in CLN2; it is thus an enzyme replacement therapy. The product is administered into the cerebrospinal fluid (CSF) by a catheter that is implanted into the lateral cerebral ventricle of the non-dominant hemisphere of the brain.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the urgent clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes the most clinically impactful publication, identified using a literature search strategy defined by the clinical lead. This publication is summarised below.


Results from a phase 1/2 dose escalation study (Study 190-201) and its open label extension (Study 190-202) have been published as a European Public Assessment Report (EPAR).

Study 190-201 and its extensions were a single arm, open label study. The study excluded patients who were aged less than 3 years or more than 16 years at enrolment, and those who required ventilation support other than non-invasive support at night. Results were compared with a historic cohort.

The primary endpoint was the score on the 6-point adapted CLN2 motor-language scale (ML scale), specifically the within-subject estimate of slope, reflecting the rate of decline in the ML scale over time.

The analysis population was 23 subjects who received cerliponase alfa and reported any efficacy results. These excluded one subject who withdrew from the study after a single infusion of study drug during the Dose Escalation Period due to inability to continue with study procedures.

The primary analysis was a responder analysis based on this population.

The ML scale is a six point scale based on two domains, each scored from 0 – 3 as follows:

<table>
<thead>
<tr>
<th>Motor domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Grossly normal gait</td>
</tr>
<tr>
<td>2</td>
<td>Abnormal gait; independent≥10 steps. Frequent falls, obvious clumsiness</td>
</tr>
<tr>
<td>1</td>
<td>No unaided walking or crawling only. Cannot walk 10 unassisted steps.</td>
</tr>
<tr>
<td>0</td>
<td>Immobile, mostly bedridden</td>
</tr>
</tbody>
</table>
### Language domain

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Grossly normal</td>
</tr>
<tr>
<td>2</td>
<td>Has become recognizably abnormal (worse than the individual maximum)</td>
</tr>
<tr>
<td>1</td>
<td>Hardly understandable</td>
</tr>
<tr>
<td>0</td>
<td>Unintelligible or no language</td>
</tr>
</tbody>
</table>

#### Primary endpoint

The mean ML score decreased by 0.4 points over a 48 week stable treatment period with cerliponase alfa 300 mg administered every 14 days. When compared to the expected rate of decline based on natural history (2 points per 48 weeks), this was statistically significant (p < 0.0001). The decline of 0.4 points was from a ML score of 3.5 points at baseline to 3.1 points at 48 weeks.

If response to treatment is defined as absence of an unreversed two-point decline in ML score at 48 weeks, 20/23 (87%) of subjects were responders.

In exploratory analyses there was a 10.9% improvement in a CLN2-based quality of life score, and a 4.3% improvement in the PedsQL generic core scale (Parent report for toddlers).

#### Safety

Eleven serious adverse events (SAEs) in 8 subjects were assessed by the investigator as related to treatment with cerliponase alfa - 9 SAEs of hypersensitivity and 2 SAEs of infusion related reaction. All 11 drug-related SAEs resolved with appropriate medical management, and all subjects with drug-related SAEs tolerated subsequent dosing and remained in the study.

No deaths were reported during study drug treatment or during follow-up in either study 201 or 202.

#### Summary of evidence

There is difference between the intervention group and the comparator which is clinically significant and not due to chance (P < 0.0001); the treatment group showed a slower rate of decline in motor and language function. There was indicative evidence of a 5% - 10% improvement in quality of life.

The drug does not impact on epilepsy, which was present in 75% of subjects.

An open label trial with a historic cohort used as comparator is a weak methodology with a high risk of bias.
4 Commissioning Position

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indications and clinical criteria listed.

Clinical commissioning policy development plan

It has been concluded that the development of a full clinical commissioning policy is not needed at this time. The longer term commissioning position will be confirmed following appraisal of cerliponase alfa by the National Institute for Health and Care Excellence (NICE).

5 Mechanism for funding

Not applicable.

6 Date of policy statement approval and review

The policy statement is effective from August 2017.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Clinical Panel of this urgent clinical commissioning policy statement then a new ‘Preliminary Policy Proposition’ should be submitted. For guidance email england.specialisedcommissioning@nhs.net.

This policy statement will be formally reviewed after the outcome of the NICE appraisal.

7 References