Carglumic acid (Carbaglu) for hyperammonaemia in organic acidaemias

September 2010

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Carglumic acid (Carbaglu) for hyperammonaemia in organic acidaemias

Target group
Branced chain organic acidaemias (acute phase or acute metabolic decompensation):
- Isovaleric acidaemia (IVA)
- Propionic acidaemia (PA)
- Methylmalonic acidaemia (MMA)

Hyperammonaemia is defined as a plasma ammonium concentration which exceeds the age-related reference range for the laboratory performing the test and is usually greater than:
- 150 μg/dL in neonates;
- 70 μg/dL in infants to one month of age;
- 35-50 μg/dL in older children and adults.

Background
Organic acidaemias (or organic acidurias) are a group of inherited autosomal recessive genetic disorders in which there is a defect in a specific step in amino acid catabolism. Each organic acidaemia is a consequence of a different enzyme defect that results in difficulty in metabolising different groups of branched-chain amino acids or lysine.

Organic acidaemias are characterised by an acute or progressive neurological deterioration caused by accumulation of toxic acids in the blood and tissues. Onset of the disease is usually in the neonatal period but a later-onset form can occur with symptoms appearing during the first years of life. Neonates usually present within the first few days of life with a toxic encephalopathy with poor feeding, vomiting, weight loss, lethargy, hypotonia, and coma, severe brain damage or death, if not promptly treated. Symptoms in the later-onset form are more variable and can include acute encephalopathy, loss of intellectual function, intermittent ataxia, recurrent keto-acidosis, psychiatric problems, poor feeding, vomiting and failure to thrive. Hyperammonaemia is a common complication of the acute phase, or during an episode of metabolic decompensation e.g. from infection, dietary change or vomiting.

Technology description
Carglumic acid (Carbaglu, N-carbamoyl-L-glutamate, NCG) is a structural analogue of N-acetylglutamate, which is a naturally occurring and selective activator of carbamoyl phosphate synthetase (CPS 1), the first enzyme of the urea cycle. Carglumic acid enhances ammonia detoxification through activation of the urea cycle and the increase of ureagenesis. Carglumic acid is intended as adjunctive therapy to specific organic acidaemia treatment, alone or concomitantly to existing ammonia-lowering agents in the acute phase. It is administered orally or via a nasogastric tube.

Carglumic acid has been approved in the EU since 2003 for the treatment of hyperammonaemia due to NAGS (N-acetyl-glutamate-synthase) deficiency in neonates, children and adults. The dose in this indication is 100-250mg/kg/day. A common side effect of carglumic acid is increased sweating.
Innovation and/or advantages

If successful at licensing availability of carglumic acid could be increased. Costs may be additional in certain cases, but are relatively low. Benefits could include a reduced need for extracorporeal therapies and their associated costs.

Developer

Orphan Europe.

Availability, launch or marketing dates, and licensing plans

Carglumic acid is a designated orphan drug in the EU for hyperammonaemia associated with PA, MMA, and IVA.

NHS or Government priority area

None identified.

Relevant guidance


Clinical need and burden of disease

Organic acidaemias such as IVA, PA, and MMA are very rare diseases. In a non-screened population such as in England and Wales, the incidence of IVA, PA and MMA combined is estimated at 0.88-1.58 cases per 100,000 births5 (7-11 cases per year in England and Wales). The prevalence of IVA, PA and MMA in the EU is estimated at 0.01, 0.02 and 0.02 per 10,000 respectively5,6,7, which equates to around 274 people in England and Wales8.

The long-term outcomes of people with organic acidaemias are poor, with progressive neurocognitive deterioration and complications such as organ impairment, for example cardiomyopathy, pancreatitis and renal failure2. There is also a high risk of basal ganglia stroke and severe motor disabilities with repeated episodes of acute metabolic decompensation2. Management of the acute phase and metabolic decompensation is a medical emergency and is usually performed in intensive care units2.

Existing comparators and treatments

Current treatments for hyperammonaemia include:

• high-energy and protein-free nutrition
• ammonia scavengers e.g. sodium benzoate (IV), or sodium phenylbutyrate (IV)
• carglumic acid (100-250mg/kg/day as a single oral dose, off-licence)
• dialysis

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>PA-associated hyperammonaemia</th>
<th>NAGS deficiency or PA-associated hyperammonaemia</th>
<th>PA-associated hyperammonaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Status</td>
<td>Published.</td>
<td>Published.</td>
<td>Published.</td>
</tr>
<tr>
<td>Location</td>
<td>Turkey.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=1; 4 month old female, on protein-restricted diet and L-carnitine supplementation; organic acidaemia; decompensated hyperammonaemia 451µg/dL. Received NCG for 4 days on an out-patient basis.</td>
<td>n=19; 1 hyperammonaemia due to NAGS deficiency (aged 57 yrs); 1 hyperammonaemia due to PA (aged 6 yrs) plus 17 healthy controls. Received NCG 2.2g/m² per day for 3 days.</td>
<td>n=7; 15 months to 13 years; hyperammonaemia due to PA. Received NCG 100mg/kg per day or 2.2g/m² per day if ≥25kg for 3 days.</td>
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<tr>
<td>Follow-up</td>
<td>1 week.</td>
<td>3 days.</td>
<td>3 days.</td>
</tr>
<tr>
<td>Key results</td>
<td>Decrease in plasma ammonia from 451µg/dL on day 1; to 320µg/dL at day 2; 191µg/dL at day 4; 68µg/dL at day 6 (normal range, 10-80µg/dL).</td>
<td>NAGS deficiency, PA and controls: increased levels of [¹³C]urea (ureagenesis). NAGS deficiency: decreased plasma levels of ammonia.</td>
<td>After NCG: peak [¹³C]urea increased from 2.2 to 3.8µM; p&lt;0.0005. Decreases in mean plasma ammonia and glutamine: 59 to 43µM; p&lt;0.018 and 552 to 331µM; p&lt;0.0005.</td>
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<tr>
<td>Trial</td>
<td>Neonatal organic acidaemia-associated hyperammonaemia</td>
<td>NCT00843921; NCG single arm study, phase II/III.</td>
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<tr>
<td>Sponsor</td>
<td>-</td>
<td>Childrens Research Institute.</td>
<td></td>
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<tr>
<td>Status</td>
<td>Trial complete, published in abstract.</td>
<td>Ongoing.</td>
<td></td>
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<tr>
<td>Source of information</td>
<td>Publication¹⁰, manufacturer.</td>
<td>Trial registry¹¹.</td>
<td></td>
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<tr>
<td>Location</td>
<td>France.</td>
<td>USA.</td>
<td></td>
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<tr>
<td>Design</td>
<td>Case series.</td>
<td>Uncontrolled, non-randomised, single arm, open-label.</td>
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<td>Participants and schedule</td>
<td>n=8; hyperammonaemia. NCG alone or in combination with other treatments.</td>
<td>N=4 (planned); aged 1 day to 70 years; one of NAGS deficiency, CPS I, ornithine transcarbamylase (OTC) deficiency, PA or MMA; recurrent hyperammonaemic episodes. 3 days of NCG 100mg/kg per day or 2.2g/m² per day if ≥25kg.</td>
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<tr>
<td>Follow-up</td>
<td>During decompensation stage.</td>
<td>3 days.</td>
<td></td>
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<tr>
<td>Primary outcomes</td>
<td>Plasma ammonia.</td>
<td>Rate of ureagenesis determined by isotopic enrichment and plasma concentration of ammonia, urea and amino acids.</td>
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<tr>
<td>Key results</td>
<td>In 2 patients, ammonia levels decreased rapidly and normalised after 10 hrs. All other patients required further medical treatment or haemofiltration.</td>
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<tr>
<td>Expected reporting date</td>
<td>-</td>
<td>Not known.</td>
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**Estimated cost and cost impact**

The cost to treat an episode of hyperammonaemia (assuming the same costs as for NAGS deficiency) is¹⁴.
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (^a)</th>
<th>3 day treatment cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carglumic acid</td>
<td>• 100-250mg/kg/day</td>
<td>neonate (3.5kg) £583.20 - £729.00 child (20kg) £1,458 - £3,645</td>
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<tr>
<td>Sodium benzoate (IV)</td>
<td>• Loading dose 250mg/kg over 90 mins</td>
<td>neonate (3.5kg) £50.24 - £75.36</td>
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<td></td>
<td>• Maintenance (day 1) dose 250mg/kg over 22.5 hrs</td>
<td>child (20kg) £251.20 - £376.80</td>
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<td></td>
<td>• Subsequent days 250mg – 500mg/kg/day</td>
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<tr>
<td>Sodium phenylbutyrate (IV)</td>
<td>• Loading dose 250mg/kg over 90 mins</td>
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<tr>
<td></td>
<td>• Subsequent days 250mg – 500mg/kg/day</td>
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</tbody>
</table>

**Claimed or potential impact – speculative**

**Patients**

- [ ] Reduced mortality or increased length of survival
- [ ] Reducing in associated morbidity or improved quality of life for patients and/or carers
- [ ] Quicker, earlier or more accurate diagnosis or identification of disease
- [ ] None identified
- [ ] Other:

**Services**

- [ ] Increased use
- [ ] Service organisation
- [ ] Staff requirements
- [ ] Decreased use
- [ ] Other:
- [ ] None identified

**Costs**

- [ ] Increased unit cost compared to alternative
- [ ] New costs: additional to current options
- [ ] Increased costs: more patients coming for treatment.
- [ ] Increased costs: capital investment needed
- [ ] Savings: potential reduction in extracorporeal therapies.
- [ ] Other:

**References**


\(^a\) Assuming wastage.


