CARBAGLU 200 mg, dispersible tablets
B/5 (CIP: 34009 365 659 2 0)
B/15 (CIP: 34009 564 102 8 6)
B/60 (CIP: 34009 564 103 4 7)

CARBAGLU 200 mg, scored dispersible tablets
B/15 (CIP: 34009 589 207 8 3)
B/60 (CIP: 34009 589 199 5 4)

Applicant: Orphan Europe

<table>
<thead>
<tr>
<th>INN</th>
<th>Carglumic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2012)</td>
<td>A16AA05 (amino acids and derivatives)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Variations to conditions for inclusion</td>
</tr>
<tr>
<td>List concerned</td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
</tbody>
</table>

Indications concerned
“Carbaglu is indicated in treatment of:
- hyperammonaemia due to isovaleric acidaemia.
- hyperammonaemia due to methylmalonic acidaemia.
- hyperammonaemia due to propionic acidaemia.”
<table>
<thead>
<tr>
<th>Actual benefit</th>
<th>Substantial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in actual benefit</td>
<td>In isovaleric or methylmalonic or propionic organic acidaemias, during the initial acute episode and subsequent episodes of decompensation with hyperammonaemia, treatment with carglumic acid (CARBAGLU 200 mg, dispersible tablet or scored dispersible tablet) instituted as swiftly as possible as first-line therapy, usually as a component of an overall treatment strategy aimed at quickly and efficiently normalizing blood ammonia levels, offers a substantial improvement in actual benefit (level II) in the treatment strategy.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>In isovaleric or methylmalonic or propionic organic acidaemias, during the initial acute episode and subsequent episodes of decompensation with hyperammonaemia, treatment with carglumic acid (CARBAGLU 200 mg, dispersible tablet or scored dispersible tablet) should be instituted as swiftly as possible as first-line therapy, usually as a component of an overall treatment strategy aimed at quickly and efficiently normalizing blood ammonia levels.</td>
</tr>
<tr>
<td>Recommendations</td>
<td>-</td>
</tr>
</tbody>
</table>
## Administrative and Regulatory Information

| Marketing Authorisation (procedure) | Initial date (centralised procedure): 24 January 2003  
|                                   | Extension of the indications: 27 May 2011  
|                                   | Risk Management Plan  
| Prescribing and dispensing conditions / special status | List I  
|                                   | For hospital prescription  
|                                   | Medicinal product included on the list provided for in Article L5126-4 of the French Public Health Code (“retrocession” list regulating the dispensing of drugs to outpatients by hospital pharmacies) and on the list of proprietary medicinal products refunded by national health insurance over and above hospitalisation benefits in accordance with Article L162-22-7 of the Social Security Code (list except for T2A)  
|                                   | Orphan medicinal product  

### ATC Classification

<table>
<thead>
<tr>
<th>Year</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>A</td>
<td>Alimentary tract and metabolism</td>
</tr>
<tr>
<td></td>
<td>A16</td>
<td>Other alimentary tract and metabolism products</td>
</tr>
<tr>
<td></td>
<td>A16A</td>
<td>Other alimentary tract and metabolism products</td>
</tr>
<tr>
<td></td>
<td>A16AA</td>
<td>Amino acids and derivatives</td>
</tr>
<tr>
<td></td>
<td>A16AA05</td>
<td>Carglumic acid</td>
</tr>
</tbody>
</table>

## Background

On 2 July 2003, after examination of the application for inclusion of CARBAGLU in the indication for treatment of hyperammonaemia secondary to N-acetylglutamate synthase (NAGS) deficiency, the Transparency Committee concluded that:
- the actual benefit is substantial,
- CARBAGLU represents a major therapeutic advance in the treatment of NAGS deficiency,
- the use of CARBAGLU for diagnostic and therapeutic (test) purposes involves 20 patients per year.

On 27 May 2011, an extension to the indication for CARBAGLU was granted for the treatment of hyperammonaemia secondary to organic acidaemias (isovaleric, methylmalonic, propionic). The company is not applying for inclusion, but is notifying the Committee of these changes to the conditions for inclusion, which comprise three new indications.

Carglumic acid is a structural analogue of the natural activator of the first enzyme in the urea cycle.

## Therapeutic Indications

“CARBAGLU is indicated in treatment of:
- hyperammonaemia due to N-acetylglutamate synthase (NAGS) primary deficiency.
- hyperammonaemia due to isovaleric acidaemia.
- hyperammonaemia due to methylmalonic acidaemia.
- hyperammonaemia due to propionic acidaemia.”
04 DOSAGE

“CARBAGLU treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders.”

“For isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia: The treatment should start upon hyperammonaemia in organic acidaemia patients. The initial daily dose should be 100 mg/kg, up to 250 mg/kg if necessary. It should then be individually adjusted in order to maintain normal ammonia plasma levels.

Method of administration:
Based on pharmacokinetic data and clinical experience, it is recommended to divide the total daily dose into two to four doses to be given before meals or feedings. The divisibility of the tablets in halves allows most of the required posology adjustments. Occasionally, the use of quarter tablets may also be useful to adjust the posology prescribed by the physician. The tablets must be dispersed in a minimum of 5-10 ml of water and ingested immediately or administered by fast push through a syringe via a nasogastric tube. The suspension has a slightly acidic taste.”

05 THERAPEUTIC NEED

Organic acidaemias are hereditary metabolic diseases associated with an enzyme deficiency in the breakdown of branched-chain amino acids (valine, isoleucine, methionine, threonine) resulting in accumulation of abnormal metabolites in urine and impacting in particular on the first step of the urea cycle through inhibition of the activity of the enzyme N-acetylglutamate synthase (NAGS).

The diagnosis is generally made during the initial acute episode, which is manifested as a metabolic encephalopathy with intoxication-type symptoms, most often in the neonatal period, and is always associated with hyperammonaemia caused by inhibition of NAGS activity by toxic precursors. Organic acidaemias are fatal without emergency administration of appropriate specific treatment where there is a suspected diagnosis of the neonatal form. Later-onset forms are accompanied by severe sequelae, in particular psychomotor disturbances. There are also life-threatening cardiac and pancreatic complications in propionic acidaemias and renal complications in methylmalonic acidaemias.

To avoid irreversible sequelae, especially neurological ones, treatment of hyperammonaemia is an absolute medical emergency. Treatment needs to be vigorous and immediate, through stopping protein intake, administration of high-dose intravenous glucose to counter catabolism, treatment of acidosis, and scavenging of toxic intermediates through administration of carnitine or L-glycine (in the case of isovaleric acidaemia). After treatment of the acute phase, chronic management is necessary, with a strict low-protein diet tailored to the particular type of organic acidaemia, administration of carnitine and/or L-glycine (for isovaleric acidaemia only) and, in some cases, metronidazole (for propionic acidaemia only).

Even with appropriate chronic management, episodes of decompensation (with or without hyperammonaemia) requiring emergency treatment can occur in the event of catabolic stress, an infection or after a meal very rich in protein.
The frequency of episodes of decompensation is poorly documented. In the retrospective study that led to CARBAGLU being granted European Marketing Authorisation, 41 patients with a mean follow-up period of 14.8 years had a total of 48 hyperammonaemia episodes (1.2 episodes per patient in 15 years, i.e. fewer than 0.1 episodes per year), suggesting a low prevalence of such recurrences.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are no medicinal products indicated in the treatment of:
- hyperammonaemia due to isovaleric acidaemia.
- hyperammonaemia due to methymalonic acidaemia.
- hyperammonaemia due to propionic acidaemia.

The proprietary medicinal product AMMONAPS (sodium phenylbutyrate), in the form of tablets or granules, is indicated as adjuvant treatment in the long-term treatment of urea cycle disorders involving deficiency in carbamoyl phosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.

It is indicated both in neonatal forms (complete enzyme deficiencies presenting in the first 28 days of life) and patients with late-onset forms (partial enzyme deficiencies presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

06.2 Other health technologies

Not applicable.

▶ Conclusion

There is no clinically relevant comparator.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Not applicable
## 08 SUMMARY OF PREVIOUS ASSESSMENTS

| Date of Opinion | 2 July 2003  
|                 | (Inclusion on the list of medicines approved for hospital use)  
| Indication | Treatment of hyperammonaemia due to N-acetylglutamate synthase (NAGS) deficiency.  
| **AB**  
| (wording) | NAGS deficiency is an extremely rare, chronic autosomal recessive disease characterised by hyperammonaemia which, if severe and/or prolonged, leads to cerebral oedema, usually followed by death. Patients who survive generally show pronounced mental retardation. Left untreated, the neonatal form progresses spontaneously to coma and then death in 90% of cases. Late-onset forms lead to mental retardation and to retarded growth and development, and even death in nearly 60% of cases.  
| **IAB**  
| (wording) | This proprietary medicinal product is intended as diagnostic and symptomatic treatment. The efficacy/adverse effects ratio for this proprietary medicinal product is high. This proprietary medicinal product is a first-line treatment. Alternatives are available, but they are less specific. The actual benefit is substantial.  
| Studies requested | -  

| Date of Opinion | 21 September 2005  
|                 | (Inclusion on the list of medicines approved for use by hospitals in addition to the box of 60 and box of 15 presentations)  
| Indication | Treatment of hyperammonaemia due to N-acetylglutamate synthetase deficiency.  
| **AB**  
| (wording) | The actual benefit of this proprietary medicinal product is substantial.  
| **IAB**  
| (wording) | No IAB (IAB V) compare to already available presentations.  
| Studies requested | -  

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HAS - Medical, Economic and Public Health Assessment Division  
6/14
09 ANALYSIS OF AVAILABLE DATA

The extension of the indication is based on a retrospective observational study involving 57 patients.

09.1 Efficacy

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Retrospective observational study of CARBAGLU in episodes of decompensation in organic acidaemias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date and duration of the study</td>
<td>July 2009 to October 2010</td>
</tr>
<tr>
<td>Study objective</td>
<td>Evaluation of blood ammonia concentration following treatment with carglumic acid in patients with hyperammonaemia secondary to an episode of decompensation of an organic acid.</td>
</tr>
</tbody>
</table>
| Inclusion criteria      | - Confirmed diagnosis of organic acidaemia (isovaleric, methylmalonic, propionic)  
                          - Blood ammonia > 60 µmol/l prior to treatment with carglumic acid  
                          - Hyperammonaemia associated with an episode of decompensation treated with carglumic acid. |
| Non-inclusion criteria  | - Confirmed or suspected diagnosis different to those listed above (i.e. organic acidaemia (isovaleric, methylmalonic, propionic))  
                          - Severe hepatic impairment  
                          - Non-acquired liver malformation  
                          - Intercurrent illness (other than organic acidaemia) giving rise to hyperammonaemia by itself |
| Study size and location | 21 centres (10 in Spain, 4 in France, 2 in Italy and Turkey, 1 in Germany, the Netherlands, United Kingdom) |
| Study products          | Carglumic acid: 100-250 mg/kg/day in 2 or 3 doses                                                    |
| Primary efficacy endpoint | Change in blood ammonia concentration relative to baseline following an episode of decompensation treated with carglumic acid |
| Secondary endpoint(s)  | Biochemical parameters: amino acids in plasma (chromatography), organic acids in urine and plasma, bicarbonate, ketone bodies in urine and plasma  
                          Clinical parameters: neurological, psychiatric, psychomotor, respiratory, hepatic. |
| Sample size             | Number of patients included: 57.                                                                    |
| Duration of follow-up   | The data were collected between January 1995 and October 2009, i.e. over a period of 14.8 years.     |

Results

**Principal characteristics of the patients included**

57 patients were included in the study:
- 41 patients (= 48 episodes) in the efficacy analysis (after exclusion of major deviations from the protocol),
- 57 patients (= 67 episodes) in the safety analysis.

A total of 19 patients (46.3%) were female and 22 (53.7%) were male.

Of the 41 patients included in the efficacy analysis, 4 (9.8%) had isovaleric acidaemia, 21 (51.2%) methylmalonic acidaemia and 16 (39.0%) propionic acidaemia. The initial episode of decompensation occurred in neonates in 28 cases (68.3%). A total of 13 patients were over four weeks old at the time of the first episode of decompensation (from one month to 22 years, with just one adult patient included).

The median age of occurrence of the episodes was 9.0 days, the mean age was 19.8 months.

The median duration of the episodes was 6 days in neonates and 7 days in patients aged over four weeks.
A total of 34 (82.9%) patients had had just one episode of decompensation treated with carglumic acid, 6 (14.6%) had had two episodes and 1 (2.4%) had had three episodes.

The mean time from onset of the episode to treatment with carglumic acid was 3 days (4.2 days for propionic acidaemia, 2.5 days for methylmalonic acidaemia, 0.8 days for isovaleric acidaemia), 1.5 days among neonates and 5.3 days in the group of older patients.

The mean first administered dose of carglumic acid was 96.3 mg/kg (13.3-303.0 mg/kg).

The duration of treatment was between 1 and 15 days, with an average of 5.5 days: 5.2 days (1-15) in propionic acidaemia, 6.1 days (1-15) in methylmalonic acidaemia and 3.5 days (2-5) in isovaleric acidaemia. The mean duration of treatment was 4.9 days in neonates and 6.5 days in older patients. The reason for stopping treatment was the end of the episode of decompensation in 86.7% (n = 39) of cases, death in 4.4% (n = 2) of cases (2 patients with methylmalonic acidaemia), and a different reason in 8.9% (n = 4) of cases.

In 21 episodes (43.8%) an ammonia scavenger (sodium benzoate or sodium phenylbutyrate) had been administered before treatment with carglumic acid or concomitantly.

**Primary efficacy endpoint**

Mean blood ammonia concentrations were 350.7 µmol/l at inclusion and 58.5 µmol/l post-treatment (Table 1).

### Table 1: Change in blood ammonia concentration

<table>
<thead>
<tr>
<th></th>
<th>Isovaleric acidaemia</th>
<th>Methylmalonic acidaemia</th>
<th>Propionic acidaemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
<td>N = 4</td>
<td>N = 25</td>
<td>N = 19</td>
<td>N = 48</td>
</tr>
</tbody>
</table>

#### Blood ammonia concentration at inclusion [µmol/l]

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovaleric acidaemia</td>
<td>666.8 (692.2)</td>
<td>435.0</td>
<td>[164.0-1633.0]</td>
<td>52.5 (28.4)</td>
<td>45.0</td>
<td>[27.0-93.0]</td>
</tr>
<tr>
<td>Methylmalonic acidaemia</td>
<td>296.9 (206.2)</td>
<td>247.8</td>
<td>[76.1-868.0]</td>
<td>67.7 (36.4)</td>
<td>58.0</td>
<td>[15.0-158.0]</td>
</tr>
<tr>
<td>Propionic acidaemia</td>
<td>355.0 (326.8)</td>
<td>213.0</td>
<td>[76.0-1200.0]</td>
<td>47.8 (20.4)</td>
<td>42.0</td>
<td>[17.0-91.0]</td>
</tr>
<tr>
<td>Total</td>
<td>350.7 (321.3)</td>
<td>215.0</td>
<td>[76.0-1633.0]</td>
<td>58.5 (31.3)</td>
<td>52.0</td>
<td>[15.0-158.0]</td>
</tr>
</tbody>
</table>

#### Plasma ammonia ≤ 60 µmol/l

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovaleric acidaemia</td>
<td>4 (100%)</td>
<td>25 (100%)</td>
<td>19 (100%)</td>
<td>48 (100%)</td>
</tr>
<tr>
<td>Methylmalonic acidaemia</td>
<td>1 (25.0%)</td>
<td>12 (48.0%)</td>
<td>5 (26.3%)</td>
<td>18 (37.5%)</td>
</tr>
<tr>
<td>Propionic acidaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Plasma ammonia > 60 µmol/l

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovaleric acidaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylmalonic acidaemia</td>
<td>1 (25.0%)</td>
<td>12 (48.0%)</td>
<td>5 (26.3%)</td>
<td>18 (37.5%)</td>
</tr>
<tr>
<td>Propionic acidaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SD**: standard deviation

The mean blood ammonia concentration at inclusion was 468.3 µmol/l [96.0 to 1633.0 µmol/l] in neonates and 171.3 µmol/l [76.0 to 385.0 µmol/l] in patients aged over four weeks.

The mean blood ammonia concentration post-treatment was 60.7 µmol/l in neonates and 55.2 µmol/l in patients aged over four weeks. The mean decrease in blood ammonia relative to baseline was -407.6 µmol/l in neonates and -116.1 µmol/l in patients aged over four weeks.

The median time taken to reach the target blood ammonia concentration (≤ 60 µmol/l) was 36.5 h (1.5 days) after the start of treatment with carglumic acid and the mean was 58.7 h (2.4 days).

A total of 73.8% of episodes treated with carglumic acid achieved the clinical target within 2 days.
Secondary endpoints
Biochemical parameters
Before commencing treatment, the plasma levels of certain amino acids (glycine, lysine, tyrosine) were elevated in neonates. Propionylcarnitine concentrations were elevated irrespective of age. Bicarbonate levels (a marker for metabolic acidosis) were lowered in 80% of neonates and in nearly half of the older patients. Abnormal plasma ketone concentrations were seen in all neonates and in half of the older patients.
After treatment with carglumic acid, amino acid and bicarbonate concentrations were normalised. No data were available for the plasma ketone concentrations after treatment with carglumic acid.

Clinical parameters
The principal clinical signs and neurological signs of the episode of decompensation regressed during treatment (Table 2). In 8.5% of cases the patient did not exhibit neurological disturbances. Coma occurred in eight episodes.

<table>
<thead>
<tr>
<th>Table 2: Principal clinical and neurological signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment (Number of patients)</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong></td>
</tr>
<tr>
<td>N = 48</td>
</tr>
<tr>
<td>Muscular hypotonia</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Poor sucking</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>Neurological signs</strong></td>
</tr>
<tr>
<td>N = 46</td>
</tr>
<tr>
<td>Somnolence</td>
</tr>
<tr>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Confusion or disorientation</td>
</tr>
</tbody>
</table>

09.2 Safety/Adverse effects

09.2.1 Safety data from the retrospective study
The safety population comprised 57 patients treated with at least one dose of carglumic acid. The duration of treatment ranged from 1 to 16 days, with a mean of 5.3 days (median: 4.0 days). The first dose of carglumic acid was between 10 and 303 mg/kg, with a mean of 86.5 mg/kg (median 62.9).
The reported adverse events are categorised according to type in Table 3.

<table>
<thead>
<tr>
<th>Table 3: Adverse events (safety population)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of events</strong></td>
</tr>
<tr>
<td>All adverse events (AEs)</td>
</tr>
<tr>
<td>AEs connected with treatment</td>
</tr>
<tr>
<td>Severe AEs</td>
</tr>
<tr>
<td>Serious AEs</td>
</tr>
<tr>
<td>Serious AEs connected with treatment</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>
A total of 7 patients presenting 11 AEs died. The retrospective nature of the study did not facilitate analysis of the causes of death. The 11 AEs were: cardiogenic shock (1 case), aggravation of the pathology (2 cases), death (1 case), multiple organ failure (1 case), hyperglycaemia (1 case), hyperlactacidaemia (1 case), methylmalonic aciduria (1 case), nervous system disorder (1 case), respiratory arrest (1 case), respiratory infection (1 case). A connection between death and the treatment was, however, ruled out by the investigators, except in a single case in which the patient died six days after stopping treatment (which had lasted nine days) following neurological disturbances (present before the start of treatment) and respiratory arrest. The investigators considered that the neurological disturbances had been connected with carglumic acid treatment.

The serious adverse events (not including the 11 that occurred in the patients who died) were:
- disseminated intravascular coagulation (1 event),
- cardiac arrest (1),
- cardiorespiratory arrest (1),
- diarrhoea (1),
- hepatic disorder (1),
- infection (1),
- drug toxicity (2),
- liver enzyme elevations (1),
- encephalopathy (1),
- anuria (1),
- respiratory failure (1).

For 5 events (cardiac arrest, diarrhoea, liver enzyme elevations, aggravation of encephalopathy, respiratory failure), the causality was unknown or was not reported. For the other events, carglumic acid was not implicated.

09.2.2 Safety data from SPC

The SPC mentions the following adverse events in organic acidaemias:
- Cardiac disorders: bradycardia (uncommon)
- Gastrointestinal disorders: diarrhoea, vomiting (uncommon)
General disorders and administration site conditions: pyrexia (uncommon)

09.2.3 Risk Management Plan

This proprietary medicinal product has a risk management plan that includes specific monitoring of the following “important” risks:
- Potential risks: lack of efficacy owing to unconfirmed diagnosis of metabolic disease or to an inadequate dose that was too low.
- Missing information: bradycardia, effects linked to pyrexia, interactions with other medicinal products and with foods, effects on pregnancy and on fetus.

09.3 Usage/prescription data

Not applicable.
09.4 Summary & discussion

The extension of the indications for treatment with carglumic acid (CARBAGLU) to hyperammonaemia due to isovaleric or methymalonic or propionic acidaemia is based on the retrospective observational analysis of 57 patients with a diagnosis of hyperammonaemia secondary to an organic acidaemia (= 68 episodes of decompensation). The majority of patients (68.3%) were neonates. Just one patient was over 18 years of age. The median age of occurrence of the episodes was 9.0 days, and the mean age was 19.8 months. The mean duration of treatment with carglumic acid was 5.5 days (1-15 days). Mean blood ammonia concentrations were 350.7 µmol/l at inclusion and 58.5 µmol/l post-treatment.

In 21 episodes (43.8%) treated with carglumic acid in which an ammonia scavenger (sodium benzoate or sodium phenylbutyrate) was given before or alongside treatment with carglumic acid:
- the median time taken to reach the target blood ammonia concentration (≤ 60 µmol/l) was 36.5 h (1.5 days) after the start of treatment with carglumic acid and the mean was 58.7 h (2.4 days),
- the clinical target was achieved within 2 days in 73.8% of treated episodes,
- the principal clinical signs of the episode of decompensation (muscular hypotonia, lethargy, poor sucking, vomiting, somnolence, visual disturbances, confusion or disorientation) regressed,
- 25 patients (43.9%) presented at least one adverse event, 13 (22.8%) a severe adverse event, and 13 (22.8%) a serious adverse event,
- 7 patients (12.3%) died. In one case, death following neurological disturbances and respiratory arrest was linked to treatment with carglumic acid.
010  THERAPEUTIC USE

The extension of the indication of CARBAGLU permits the treatment of the initial acute episode or subsequent episodes of decompensation with hyperammonaemia secondary to isovaleric or methylmalonic or propionic acidaemia, which are very rare metabolic diseases.

To avoid irreversible sequelae, especially neurological ones, treatment of the hyperammonaemia characteristic of these organic acidaemias is an absolute medical emergency. The treatment of the initial acute episode or subsequent episodes of decompensation with hyperammonaemia requires vigorous emergency treatment involving:
- stopping protein intake,
- enteral or parenteral administration of high-energy carbohydrates and lipids,
- treatment of dehydration, acidosis and fluid or electrolyte imbalances,
- administration of carnitine and/or L-glycine in the case of isovaleric acidaemia,
- administration of ammonia scavengers (sodium benzoate or sodium phenylbutyrate),
- renal dialysis, where necessary on account of the blood ammonia concentration.

In isovaleric or methylmalonic or propionic organic acidaemias, during the initial acute episode and subsequent episodes of decompensation with hyperammonaemia, treatment with carglumic acid (CARBAGLU 200 mg, dispersible tablet or scored dispersible tablet) should be instituted as swiftly as possible as first-line therapy, usually as a component of an overall treatment strategy aimed at quickly and efficiently normalizing blood ammonia levels.

CARBAGLU is given during the episode of decompensation with hyperammonaemia and is not a preventive treatment for isovaleric, methylmalonic or propionic organic acidaemias.
In view of all the above data and information, and following the debate and vote, the Committee’s opinion is as follows:

011.1 Actual benefit

- Organic acidaemias are characterised by an enzyme deficiency in the breakdown of branched-chain amino acids (valine, isoleucine, methionine, threonine) resulting in accumulation of abnormal metabolites in urine and impacting in particular on the first step of the urea cycle through inhibition of the activity of NAGS.
- The diagnosis is generally made during the initial acute episode, which is manifested as metabolic encephalopathy with intoxication-type symptoms, most often in the neonatal period, and hyperammonaemia. To avoid irreversible sequelae, especially neurological ones, such patients must be treated as a matter of urgency. The treatment of hyperammonaemia is an absolute medical emergency.
- These proprietary medicinal products are intended as symptomatic treatment.
- On the basis of the available data, which do not permit evaluation of the actual active role of carglumic acid in bringing down hyperammonaemia as part of the overall treatment strategy for hyperammonaemia secondary to an organic acidaemia, it is not possible to quantify the efficacy/adverse effects ratio of these proprietary medicinal products.
- There are no alternative medicinal products.
- These proprietary medicinal products are a first-line therapy.
  - Public health benefit:
    In view of the low burden represented by organic acidaemias and the absence of any established impact at population level on public health criteria (reduction in mortality or morbidity, improvement in quality of life, healthcare logistical changes, etc.), the proprietary medicinal product CARBAGLU is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of CARBAGLU is substantial in the extension of the Marketing Authorisation indications.

011.2 Improvement in actual benefit (IAB)

In isovaleric or methylmalonic or propionic organic acidaemias, during the initial acute episode and subsequent episodes of decompensation with hyperammonaemia, treatment with carglumic acid (CARBAGLU 200 mg, dispersible tablet or scored dispersible tablet) instituted as swiftly as possible as first-line therapy, usually as a component of an overall treatment strategy aimed at quickly and efficiently normalizing blood ammonia levels, offers an important improvement in actual benefit (level II) in the treatment strategy.
011.3 Target population

CARBAGLU is a treatment for the initial acute episode or subsequent episodes of decompensation with hyperammonaemia (0.1 episodes of recurrence per year per patient according to the retrospective study).

There is no national register of cases of organic acidaemias.

According to the Orphanet reports on rare diseases (June 2013), the prevalence of isovaleric acidaemia is estimated at 1 case in 100,000, that of propionic acidaemia at 0.2 cases in 100,000, and that of methylmalonic acidaemia at 1.9 cases in 100,000. Extrapolated to the French population, this represents a total of about 2000 persons.

According to an expert opinion, about 250 persons are currently being followed up at reference centres and the incidence is estimated at 20 new cases per year in France. This estimate of the incidence is consistent with data published in Italy\(^1\) with an incidence of 1.94 per 100,000 births, which would equate to 16 patients per year in France.

The total effective target population can be estimated at 45 new episodes per year in France.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the extension of the indications to “treatment of hyperammonaemia due to isovaleric acidaemia, hyperammonaemia due to methylmalonic acidaemia, hyperammonaemia due to propionic acidaemia” and at the dosages in the Marketing Authorisation.

-Packaging
Appropriate for the prescription conditions according to the indication, dosage and duration of treatment.

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