Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

carglumic acid 200mg dispersible tablets (Carbaglu®) SMC No. (899/13)

Orphan Europe (UK) Limited

06 September 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

carglumic acid (Carbaglu®) is accepted for use within NHS Scotland.

Indication under review: hyperammonaemia due to isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia.

The available clinical evidence for carglumic acid, although limited, suggests that plasma ammonia is reduced rapidly to non-toxic levels in life-threatening situations where rapid initiation of treatment is essential.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 October 2013

Indication

- hyperammonaemia due to isovaleric acidaemia
- hyperammonaemia due to methylmalonic acidaemia
- hyperammonaemia due to propionic acidaemia

Dosing Information

Carglumic acid treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders.

The initial daily dose should be 100mg/kg, up to 250mg/kg if necessary. It should then be individually adjusted in order to maintain normal ammonia plasma levels.

The total daily dose should be divided into two to four doses and given before meals or feedings. The tablets must be dispersed in a minimum of 5 to 10mL of water and ingested immediately or administered by fast push through a syringe via a nasogastric tube.

Product availability date

14 April 2011. Carglumic acid was granted orphan status for this condition on 7 November 2008.

Summary of evidence on comparative efficacy

Carglumic acid is an orphan medicine and the first to be licensed for the treatment of hyperammonaemia due to isovaleric acidaemia, methylmalonic acidaemia or propionic acidaemia. In the European Union, isovaleric acidaemia affects approximately 0.01 per 10,000 people, and methylmalonic acidaemia and propionic acidaemia each affects approximately 0.02 per 10,000 people.[1-3] Organic acidaemias are autosomal recessive disorders of branched-chain amino acid metabolism and patients present with high ammonia blood levels.[4] Carglumic acid is a structural analogue of N-acetylglutamate, the naturally occurring activator of carbamoyl phosphate synthetase and helps to break down ammonia, which results in reduction of blood levels and toxic effects.[1-3,5] In 2006, SMC accepted carglumic acid for restricted use for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency. The current submission is for a licence extension.

One retrospective, observational, non-comparative, multi-centre study has been conducted in 57 patients with hyperammonaemia due to an organic acidaemia decompensation episode.[4,6] Patients with confirmed organic acidaemia (isovaleric, methylmalonic or propionic) and who had reported hyperammonaemia (>60 micromoles/L) in at least one full organic acidaemia decompensation episode were included. All patients received carglumic acid; the dose and treatment duration were at the discretion of the treatment physician. The recommended initial dose is 100 to 250mg/kg/day (given in divided doses) and, in the study, the mean starting dose (day one) was 145.3mg/kg (17.9 to 909.1mg/kg)[6]. The evaluation window was defined as up to a maximum of 15 days after the first dose.

The primary outcome was to describe the biological response (ammonaemia) to treatment with carglumic acid. The endpoint was the last available value of plasma ammonia under treatment

or the last available value within 18 hours after the last dose of carglumic acid. The endpoint was assessed at discontinuation of treatment within 15 days of initiation, or on day 15 if treatment was still on-going (episode not resolved).

Following medical and data review of protocol deviations, the efficacy population included 41 patients (representing 48 episodes), comprising 28 neonates (68%) and 13 patients >4 weeks of age at the time of the first episode (32%). Four patients (9.8%) had isovaleric acidaemia, 16 (39%) had propionic acidaemia and 21 (51%) had methylmalonic acidaemia. The proportion of episodes that were treated with ammonia scavengers (before or during carglumic acid treatment) was 44% (21/48).[6] The ammonia scavenger medications used included sodium benzoate and sodium phenylbutyrate.

In the efficacy population, the mean baseline plasma ammonia was 350.7 micromoles/L (range 76 to 1,633 micromoles/L). Mean plasma ammonia at endpoint was 58.5 micromoles/L and the mean change was -292.2 micromoles/L (range -24 to -1,540 micromoles/L). The median time from initiation of carglumic acid to achieve the primary endpoint was 36.5 hours and the mean duration of treatment was 5.5 days (range 1 to 15 days).

The mean plasma ammonia at endpoint in the acidaemia sub-groups ranged from 47.8 micromoles/L to 67.6 micromoles/L and median time to achieve the primary endpoint was 36 to 40.5 hours. The mean plasma ammonia at endpoint in the sub-group of episodes treated with ammonia scavenger medication was 55.6 micromoles/L, and without ammonia scavenger medication was 60.8 micromoles/L. The mean plasma ammonia at endpoint in the neonate group was 60.7 micromoles/L, and in the non-neonate group was 55.2 micromoles/L. The median time to endpoint was longer in the neonate group (38.4 hours) than in the non-neonate group (28.3 hours).

Clinical markers, including gastrointestinal and neurological markers, ketoacidosis and hyperventilation reduced from baseline to endpoint. Symptom improvement was very similar in the neonate and non-neonate sub-groups and also in patients treated with and without ammonia scavengers.

Summary of evidence on comparative safety

The safety population included 57 patients exposed to at least one dose of study drug. A total of 74 treatment emergent adverse events were reported by 44% (25/57) of patients. Both serious adverse events and severe adverse events were reported in 23% (13/57) of patients.[6]

Overall, 24 treatment-related adverse events were recorded for nine patients (16%). These included “general disorders and administration site conditions” system organ class (16%), the “blood and lymphatic system disorders” system organ class (14%), the “infections and infestations” system organ class (12%) and the “metabolism and nutrition disorders” system organ class (12%).[6]

There were seven deaths due to adverse events and six of these were considered by the investigator to be unrelated to study treatment. One event (neurological damage) was considered by the investigator to be related; however, the sponsor assessed it as unrelated due to the patient’s pre-existing neurological symptoms.

Summary of clinical effectiveness issues

Organic acidaemia is a rare autosomal-recessive disorder resulting in high blood ammonia levels. It is life-threatening, resulting in metabolic encephalopathy with ketoacidosis, hypo- or hyperglycaemia, hyperglycinaemia, neutropenia, thrombocytopenia and protein intolerance. Restoration of biochemical and physiological homeostasis is the aim of treatment which should be initiated as soon as possible to prevent further neurological problems and requirement for haemodialysis.[4] Carglumic acid is an orphan medicine for treatment of hyperammonaemia due to isovaleric acidaemia, methylmalonic acidaemia or propionic acidaemia. Current treatments include ammonia scavengers (e.g. sodium benzoate which is available from 'special-order' manufacturers or specialist importing companies and sodium phenylbutyrate), and a low-protein diet.[1-3,7] Clinical experts consulted by SMC report the use of haemodialysis, sodium benzoate, sodium phenylbutyrate, carglumic acid and nutritional management for severe hyperammonaemia.

One non-comparative, retrospective, observational study provides efficacy data for carglumic acid in the treatment of hyperammonaemia due to organic acidaemia. In the efficacy population, plasma ammonia was reduced to a mean value of <60 micromoles/L in a median of 36.5 hours. There was no apparent difference in the symptom improvement rate between patients treated with or without ammonia scavenger medication. Furthermore, the study showed efficacy of carglumic acid in all baseline severity conditions, in the three acidaemia diagnostic categories and in all age groups. However, no statistical tests were reported for the analysis of primary or secondary endpoints.

Efficacy data are limited to the uncontrolled, retrospective observational study and no comparative data are available. However, given the rarity of the disease the European Medicines Agency (EMA) considered that the study design and population were acceptable. The EMA commented that a number of adverse events were poorly characterised but considered, overall, the safety profile to be satisfactory.

In the study, plasma ammonia concentration was required to be >60 micromoles/L prior to treatment, and the mean value at baseline was 351 micromoles/L. British inherited metabolic disease group (BIMDG) clinical practice guidance notes that during an episode of decompensation plasma ammonia concentrations are usually >100 micromoles/L, but on rare occasions may not be raised in the early stages. Urgent attention is required in patients with plasma ammonia concentrations >200 micromoles/L.

In the efficacy population, the mean duration of treatment was 5.5 days, median time to reach endpoint was 36.5 hours, and mean dose on day one was 145mg/kg. The licensed daily dose is in the range 100 to 250mg/kg initially and the dose is adjusted to maintain normal ammonia plasma levels. Due to the limited efficacy data, there is some uncertainty in terms of the dose and length of treatment that will be used in clinical practice. Clinical experts have reported treatment duration of two to seven days with carglumic acid while the BIMDG guidance recommends a single dose of 250mg/kg.

The majority of patients (83%) in the study were treated for one episode of hyperammonaemia, although seven patients went on to receive treatment for two or three episodes. However, the time period in which repeated episodes occurred is not clear. One clinical expert has reported that recurrent hyperammonaemia is unusual and therefore chronic or repeated treatments are

unlikely, while another clinical expert noted that repeated episodes of severe hyperammonaemia have been reported in some children.

Patients will require on-going monitoring whilst on carglumic acid treatment, including ammonia and amino acid plasma levels, as well as liver, renal, cardiac functions and haematological parameters. However, the close monitoring of patients is routine during the management of hyperammonaemia due to acidaemia.

The available clinical evidence for carglumic acid, although limited, suggests that plasma ammonia levels are reduced rapidly to non-toxic levels in life-threatening situations where rapid initiation of treatment is essential, and where there is currently unmet need.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of carglumic acid as an adjunct to usual care, consisting of medical therapy with arginine, sodium benzoate or sodium phenylbutyrate, compared to usual care alone for the treatment of hyperammonaemia due to isovaleric acidaemia, methylmalonic acidaemia or propionic acidaemia in neonates. The analysis consisted of a short term decision tree analysis with Markov extrapolation beyond 2 years to a lifetime horizon.

Based on expert clinical opinion from Scotland, carglumic acid was estimated to result in an 80% reduction in the need for haemodialysis, from a 0.71 probability of dialysis requirement with usual care to a 0.14 probability with carglumic acid. Neonates requiring haemodialysis were associated with a 33% probability of death within year 1, a 20% probability of severe neurological impairment at year 2 and a 90% probability of long term learning difficulties at the start of year 3, whilst for those requiring medical therapy alone, the probabilities were zero, 16.7% and 83.3% respectively. All these estimates were derived from a published epidemiological study in 21 infants conducted in Italy, with maximum patient follow-up to age 12.5 years.

The average cost of carglumic acid was estimated to be £536 per patient assuming that each patient will require at least one full pack of 5 x 200mg tablets to treat a single episode, and 50% will require additional doses necessitating a second pack to be opened – packs cannot be stored. Based on the observational study, 17% of neonates are assumed to receive carglumic acid for up to three episodes of hyperammonaemia, the majority having one episode. Cost estimates from published sources or ISD Scotland were used for haemodialysis and the associated use of emergency transport and special care baby unit/intensive care facilities, and the health and social care costs associated with severe neurological impairment and long term learning difficulties. Utilities associated with neurological impairment (0.524) and with learning difficulties (0.769) were derived from a published study of EQ- 5D values by ICD code, and age adjusted EQ- 5D utilities for the UK population were applied for patients without neurological impairment over the lifetime horizon of the model.

The base case result was an incremental cost per quality adjusted life year (QALY) gained of £7,652 for carglumic acid compared to usual care alone, based on an lifetime incremental cost of £26,572, incremental life years gained of 4.26 and QALYs gained of 3.47. The main benefit of carglumic acid in the model come from a reduction in neonate mortality linked to fewer patients requiring dialysis. Most of the incremental cost and lower incremental QALYs (relative

to incremental life years) estimated for carglumic acid is related to the lower probability of neonate death, which means more neonates are surviving but many are also incurring long term costs and disutility associated with severe neurological impairment or learning difficulties.

In scenario analysis, when the probability of short term neonate mortality with dialysis is decreased, the cost-effectiveness of carglumic acid improves due to higher numbers of usual care patients surviving but with long-term neurological impairment/learning difficulties. Likewise, if short term mortality with medical therapy is increased the cost-effectiveness of carglumic acid improves due to smaller numbers of carglumic acid patients surviving and incurring long-run costs and disutility associated with long-term neurological impairment/learning difficulties. Carglumic acid is also associated with an incremental cost effectiveness ratio (ICER) below £20k/QALY even if there is only a 1% reduction in dialysis requirement due to the impact of lower mortality risk. The probability of long term learning difficulties after dialysis needs to be reduced to <50%, or the short term severe neurological impairment with medical therapy alone increased to >55% for the ICER for carglumic acid to increase above £30k/QALY. Cost-effectiveness was not highly sensitive to variations in cost or utility estimates.

Overall, the economic analysis was hampered by a lack of clinical data, which is associated with the rarity of the condition. Relating to this, the key issues in the economic analysis were as follows:

- A lack of direct evidence for the effectiveness of carglumic acid on key outcomes of dialysis requirement, mortality and neurological impairment, so effectiveness was based only on expert opinion and outcomes from a small Italian epidemiological study. Hence, all the probabilities used in the economic model are highly uncertain. However, SMC clinical experts remarked that, whilst uncertain, the probabilities used were plausible.
- The time horizon of 100 years is long given the limitations of the data available for the extrapolation (small numbers, and maximum follow-up to age 12.5 years). However, in sensitivity analysis, adopting a shorter time horizon of 20 years does not have a major impact on the ICER.
- Whilst the base case ICER is acceptable at £7.7k/QALY given the limited data there is a need for extensive sensitivity analysis to explore whether there are circumstances under which carglumic acid may not be considered cost-effective. However, additional sensitivity analysis provided by the submitting company has demonstrated that only a very small reduction in dialysis, neonate mortality or severe neurological impairment/learning difficulties associated with carglumic acid relative to usual care alone is required in order for carglumic acid to achieve ICERs below £30,000/QALY.

Therefore, due primarily to the low cost per patient for treatment and expert opinion supporting the potential life saving potential of carglumic acid, it is expected that carglumic acid represents a cost-effective treatment of hyperammonaemia due to organic acidaemia in neonates.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The following current best practice guidelines are available:

BIMDG guidance on *Undiagnosed hyperammonaemia; diagnosis and immediate management* (last reviewed January 2013).[8]

Management decision should be based on clinical status and involves use of intravenous infusions of glucose/sodium chloride and medication (with sodium benzoate, sodium phenylbutyrate, arginine or carnitine). The guideline also notes that a single oral dose of N-carbamyl glutamate [carglumic acid] may be considered for N-acetylglutamate synthase deficiency and hyperammonaemia secondary to organic acidaemias.

BIMDG guidance on *Medicines used for the treatment of hyperammonaemia* (last reviewed January 2013).[9]

A single oral dose of N-carbamyl glutamate [carglumic acid] 250mg/kg may be given in an emergency.

Additional information: comparators

There are no comparators. Treatment with carglumic acid is in addition to current treatments.

Cost of relevant comparators

Drug	Dose Regimen	Patient's weight	Cost per episode (£)
Carglumic acid	**100mg/kg/day to 250mg/kg/day**	**3.5kg (neonate)**	**299 to 1,794**
		20kg (child)	**598 to 8,493**

Costs from MIMS on 1 July 2013. Costs are based on a treatment duration range of one to six days (mean duration of treatment in study was 5.5 days, however BIMDG guidance recommends one single dose). NB: the shelf life of carglumic acid, once the container is opened, is one month. Costs are therefore rounded up to multiples of five tablets as this is the smallest available pack.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 5 per year, with an estimated uptake rate of 40% per year i.e. 2 patients treated per annum.

As carglumic acid is an adjunctive treatment, no displacement of other drug therapies is assumed and so the gross and net impact on the medicines budget was estimated to be £1.07k per annum for each of years 1 to 5. However, given SMC expert feedback on use of carglumic acid in neonates, it is possible that all eligible patients would receive treatment. If all 5 eligible patients received the treatment, the expected annual budget impact would then be £2.68k.

The budget impact may be overestimated in the presence of existing use of carglumic acid for organic acidaemia.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. Public summary of positive opinion for orphan designation of carglumic acid for the treatment of isovaleric acidaemia (EU/3/08/575). 1 April 2009.
2. European Medicines Agency. Public summary of positive opinion for orphan designation of carglumic acid for the treatment of methylmalonic acidaemia (EU/3/08/576). 1 April 2009.
3. European Medicines Agency. Public summary of positive opinion for orphan designation of carglumic acid for the treatment of propionic acidaemia (EU/3/08/577). 1 April 2009.
4. European Medicines Agency. European Public Assessment Report for Carbaglu® (carglumic acid). Procedure No. EMEA/H/C/000461/II/0013
5. Orphan Europe (UK) Limited. Summary of product characteristics for carglumic acid (Carbaglu®). Last updated 6 June 2013.
6. Orphan Europe. Clinical summary in the indication; treatment of hyperammonaemia due to organic acidaemia; module 2, section 2.7.
7. British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health, and Neonatal and Paediatric Pharmacists Group. British National Formulary for Children. BMJ Group and RPS Publishing. London; June 2013
8. BIMDG. *Undiagnosed hyperammonaemia; diagnosis and immediate management*. Last reviewed January 2013. http://www.bimdg.org.uk/store/protocols/docs/Hyperammonaemiaand-managev3-2-732053-22-05-2013.pdf
9. BIMDG. *Medicines used for the treatment of hyperammonaemia*. Last reviewed January 2013. http://www.bimdg.org.uk/store/protocols/general/UCD-medicines2-330009-22-05-2013.pdf

This assessment is based on data submitted by the applicant company up to and including 27 July 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.