

carglumic acid 200mg dispersible tablets (Carbaglu[®]) No. 299/06
Orphan Europe

8 September 2006

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

carglumic acid (Carbaglu[®]) is accepted for restricted use within NHS Scotland for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency. Limited data from retrospective case analysis indicate that carglumic acid generally allowed patients to maintain normal ammonia levels, growth and psychomotor development.

Carglumic acid is restricted to use by experts providing the supraregional specialist service for this disease.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

**carglumic acid 200mg
dispersible tablets
(Carbaglu®)**

Indication

Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.

Dosing information

Initial daily dose of 100mg/kg to 250mg/kg. The dose should then be adjusted individually to maintain normal plasma ammonia levels. In the long-term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved; daily doses range from 10mg/kg to 100mg/kg. Daily dose should be divided into 2 to 4 doses before meals or feeding.

UK launch date

January 2003

Comparator medications

There are no other direct comparators for this specific enzyme deficiency. Other agents have been used as a secondary pathway: these nitrogen scavengers include sodium benzoate and sodium phenylbutyrate.

Cost of relevant comparators

The cost of treatment with carglumic acid will vary greatly depending on the individual dose required to maintain metabolic control and the body weight of the patient. The basic NHS cost is £226 for 5 x 200mg tablets and £2685 for 60 x 200mg tablets

Drug	Dose	Daily cost/kg body weight
Carglumic acid	Initial dose 100-250mg/kg	£22-£56
	Long term 10-100mg/kg	£2.24-£22

Using a daily dose of 50mg/kg (median dose at last recorded treatment in EPAR was 52mg/kg), the following annual costs could be expected:

One year old infant weighing 10kg:	£41,000
Ten year old child weighing 30kg:	£123,000
Adult weighing 60kg:	£245,000

Summary of evidence on comparative efficacy

N-acetylglutamate synthase (NAGS) deficiency is one of six recognised disorders of the urea cycle; the metabolic pathway which transforms ammonia into urea. NAGS is the enzyme responsible for the synthesis of N-acetylglutamate (NAG) which in turn activates carbamoyl phosphate synthetase, the first step in the urea cycle. NAGS deficiency results in an accumulation of ammonia, which, depending on severity, can cause irreversible brain damage and death. Carglumic acid is an analogue of NAG and has been shown to activate carbamoyl phosphate synthetase. This is a rare disorder, estimated to affect 0.00125 per 10,000 persons in the European Union (around 1 in 5 million). Hence carglumic acid was designated an orphan drug in October 2000.

Due to the rarity of this condition, there are no controlled clinical trials and the clinical evidence is limited to a retrospective patient data collection by the company. This included 20 patients who received chronic treatment with carglumic acid. Of these patients, twelve were treated for NAGS deficiency: six patients having the more severe form of neonatal presentation; three having late-onset presentation and three with no definite classification. Since there have been no dose ranging studies, the doses used have been empirical. The required dose depends on both the severity of the deficiency and the protein load. A rapid normalisation of the plasma ammonia levels is desirable, requiring a high initial dose, followed by a lower titrated dose to maintain ammonia levels within the normal range. The maximum daily dose used, which was generally the initial dose, ranged from 35 to 254mg/kg (median 133mg/kg); while the last daily dose (recorded at the last visit) ranged from 7 to 98mg/kg (median 52mg/kg). At the cut-off date (July 31 2001), the duration of treatment ranged from 0.7 to 9.8 years. Data were recorded on plasma ammonia and amino acid levels (including glutamine), physical growth, psychomotor development, clinical symptoms of acute hyperammonaemic decompensation and survival. Concomitant therapy did not appear necessary and sodium benzoate and sodium phenylbutyrate were progressively withdrawn. Arginine was continued in seven patients but their outcomes did not differ from the five who received no arginine. Diet was unrestricted or normal in half of the patients.

During treatment, ammonia levels were well controlled and were always normal in five patients and abnormal on only one occasion in three patients. There were transient fluctuations slightly above the upper normal value in three further patients and in one patient fluctuating ammonia levels never normalised but decreased during treatment. In the patients with initially elevated plasma glutamine levels, these rapidly normalised during carglumic acid therapy.

Growth was found to be normal in all patients despite being below normal in five patients before treatment. Psychomotor development was normal allowing normal school attendance in 11 patients. One patient, treated for one year, was considered mentally impaired before treatment. There was only one clinical symptom of acute hyperammonaemia in one patient due to an accidental interruption in drug supply. No deaths were reported.

There are also limited supportive data on four cases of treated patients with NAGS deficiency from the literature. Two of these patients have developed normally.

In a further study, eight patients with suspected urea cycle defects were given a test dose of carglumic acid (200mg/kg orally or via nasogastric tube) and had plasma ammonia levels monitored. In four patients, ammonia levels normalised, subsequent diagnoses of NAGS deficiency were made and treatment was continued. An analysis by the company including

information on these patients and those untreated or treated conventionally, suggests that carglumic acid has an important impact on the prognosis of NAGS deficiency.

Summary of evidence on comparative safety

From the limited data available on patients treated with the recommended doses, there have been no adverse events that could be attributed with certainty to carglumic acid. There have been cases reported of increased sweating and increased transaminases.

Summary of clinical effectiveness issues

The data available to support the efficacy of carglumic acid are very limited due to the nature of the condition. However, the patients treated appear to have experienced a treatment effect. With no treatment, these patients face neurological deterioration, coma and death. Treatments with conventional nitrogen scavenging agents are not specific for this deficiency and fail to control chronic hyperammonaemia and acute decompensation.

The doses used to treat patients have been empirical and whether those recommended will prove to be optimal remains to be seen.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis comparing carglumic acid with usual care in the treatment of NAGS deficiency. The main data source used in the analysis is retrospective patient data, with specific focus on the 5 UK patients currently being treated with carglumic acid. The manufacturer made a good attempt at presenting an economic case based on limited data and concluded that the lifetime cost per QALY was around £81,000.

The high cost associated with carglumic acid was considered to be balanced by the high benefit achieved from this treatment in patients with NAGS deficiency.

The SMC orphan drug policy requires manufacturers to make complete submissions to allow a comprehensive product assessment similar to all other drug submissions. However, in addition to the usual assessment of clinical and cost-effectiveness, SMC may consider additional factors specific to orphan and ultra-orphan products. Within this context the overall budget impact of the therapy may also be considered.

Patient and public involvement

A Patient Interest group Submission was not made.

Budget impact

There are currently only five cases of this very rare condition in the UK. The cost of treatment relates to the patient's body weight, so ranges from approximately £40K for a 1 years old child rising to £245K for a 60kg adult per annum.

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.

This assessment is based on data submitted by the applicant company up to and including 14 July 2006.

The SMC have adopted the European Agency for the Evaluation of Medicinal Products (EMA) definition of orphan medicines - an orphan medicine is one licensed for treating or preventing life-threatening rare diseases affecting fewer than 5 in 10,000 people in the European Union.

Drug prices are those available at the time the papers were issued to SMC for consideration.

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

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