5.03 CARGLUMIC ACID
200 mg tablet, 5
200 mg tablet, 20
Carbaglu®
Emerge Health

1 Purpose of Application

1.1 To request Authority Required listing for carglumic acid for treatment of acute hyperammonaemia due to organic acidaemias - isovaleric acidaemia (IVA), methylmalonic acidaemia (MMA) and propionic acidaemia (PA).

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CARGLUMIC ACID				
200mg tablet, 5	20	0	Carbaglu®	Emerge Health
200mg tablet, 60	2	0	Carbaglu®	Emerge Health

Category/program	GENERAL – General Schedule (Code GE)
Prescriber type	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity	N/A
Severity	N/A
Condition	Hyperammonaemia due to organic acidaemias such as: ○ Hyperammonaemia due to isovaleric acidaemia; ○ Hyperammonaemia due to methylmalonic acidaemia; ○ Hyperammonaemia due to propionic acidaemia
Treatment phase	N/A
Restriction level	Authority Required
Treatment criteria	Treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders. Any episode of acute symptomatic hyperammonaemia should be treated as a life-threatening emergency and may be started as early as the first day of life. Treatment of hyperammonaemia may require dialysis, preferably haemodialysis, to remove a large burden of ammonia. Uncontrolled hyperammonaemia can rapidly result in brain injury/damage or death, and prompt use of all therapies necessary to reduce plasma ammonia levels is essential.
Clinical criteria	N/A
Population criteria	N/A

Note: The submission did not provide the requested restriction in the standard table format; the information provided in the submission was placed into this format during the evaluation.

2.1 With regards to the diagnosis of organic acidaemias, the PSCR advised that "Häberle et al. (2012) indicates that after confirmation of hyperammonaemia, further biochemical tests to identify organic acids in urine must be undertaken. This will differentiate between various types of urea cycle disorders. Genetic testing is the best method to confirm the diagnosis." (PSCR). The ESC noted that it was unclear whether this genetic testing was conducted during routine neonatal screening in each state and territory.

2.2 The PSCR requested that the requested maximum quantities be 20 for the 5-tablet bottle and 2 for the 60-tablet bottle. The ESC noted that the requested maximum

quantities could present a wastage issue as patients may receive more carglumic acid than required for the duration of the decompensation episode. Furthermore, the DPMQs provided in the submission (which were based on a maximum quantity of one bottle) will not be applicable to the new maximum quantities.

2.3 The ESC noted that the PSCR did not provide a restriction in the appropriate format as requested during the evaluation.

2.4 A cost-effectiveness analysis for carglumic acid versus standard therapy in acute hyperammonaemia secondary to IVA, MMA or PA was presented.

2.5 The pre-PBAC response requested the following additional clinical criterion:

> Patients need to be experiencing hyperammonaemia due to organic acidaemias. Treatment may be initiated then confirmatory biochemical tests to determine ammonia concentration levels as well as genetic testing should be undertaken to confirm a diagnosis of organic acidaemia. If this is not conformed then ongoing PBS prescribing should be ceased.

3 Background

3.1 TGA status at time of PBAC consideration: Carglumic acid was TGA registered on 12 February 2015 for the following indications:

- Hyperammonaemia due to N-acetylglutamate synthase (NAGS) primary deficiency.
- Hyperammonaemia due to organic acidaemias (OA) such as:
  - Hyperammonaemia due to IVA;
  - Hyperammonaemia due to MMA; and
  - Hyperammonaemia due to PA.

3.2 Carglumic acid has not been considered by the PBAC previously.

4 Clinical place for the proposed therapy

4.1 PA, MMA and IVA are organic adidaemias caused by inborn errors of metabolism:

- PA is caused by a deficiency of propionyl-CoA carboxylase.
- MMA is caused by a deficiency of methylmalonyl-CoA mutase, a vitamin B12-dependent enzyme which converts 1-methylmalonyl-CoA to succinyl-CoA.
- IVA is a leucine metabolism disease due to deficiency of isovaleryl-CoA dehydrogenase.

These disorders lead to reduced NAGS activity and impairment of the urea cycle. Whilst these three deficiencies are caused by defects in different enzymes, if left untreated they will all result in hyperammonaemia. Hyperammonaemia secondary to organic acidaemia is a serious acute condition and is most common in neonates. Patients may fall into a coma and require constant monitoring, with the possible need for admission into a neonatal intensive care unit and access to haemofiltration.

4.2 The current treatment of hyperammonaemia includes low protein / protein-free diet, high calorie nutrition, arginine supplementation, ammonia scavengers (e.g. sodium benzoate, sodium phenylacetate or sodium phenylbutyrate); and haemofiltration as rescue therapy. Carglumic acid will be added to these treatments. The mean duration

of treatment with carglumic acid is assumed to be five days in the economic analysis and ranged from less than one day to 29 days in the studies presented in the submission.

4.3 The evaluation considered that it is unlikely that there would be any patients accessing carglumic acid for hyperammonaemia secondary to organic acidaemia on the PBS, given the severity and nature of the condition. Hyperammonaemia secondary to organic acidaemia is a serious acute condition which is most common in neonates, and one where patients may fall into a coma and require constant monitoring, with the possible need for admission into a neonatal intensive care unit and access to haemofiltration. Thus, it is considered unlikely that patients will be treated at home or as an outpatient in hospital setting. It is possible that patients will be treated in a private hospital, but given the possibility that patients may need admission to a neonatal intensive care unit it is more likely that patients will be treated in a large tertiary public hospital as an inpatient, meaning that they would not be eligible to receive PBS funded carglumic acid.

4.4 The Australasian Society for Inborn Errors of Metabolism (ASIEM) advised that carglumic acid has only been used in the setting of hospital admission. The ASIEM 'stressed that there is no reason to treat patients with these organic acidaemias with carglumic acid as an on-going (at home) treatment. Rather…this treatment should be restricted to specific acute situations when the metabolic physician deems it appropriate to treat a particular child at a particular time with the medication, perhaps preventing the need for haemofiltration'. However, the ASIEM also noted that the main barrier for patients to access carglumic acid is the cost of the drug.

4.5 The PSCR claimed that discussions with hospital pharmacists have confirmed that the majority of specialists treating affected metabolic patients are seeing these patients in public hospital outpatient clinics and that treatment in this setting would access the PBS.

4.6 The ESC noted that the PSCR appeared to contradict the advice from the ASIEM that carglumic acid has only been used in the setting of hospital admission. However, the ESC also noted that the advice from the ASIEM also appeared to contradict itself by stating that cost is a barrier to access for patients while claiming that all patients are receiving the drug while admitted to hospital.

4.7 As the PSCR did not provide further evidence to support the position that cost to patients is a barrier to access and that carglumic acid is used in an outpatient setting, the ESC considered that it remained unclear whether any patients currently receive carglumic acid outside of hospital admission. Accordingly, the ESC was unclear on the clinical need to list the drug on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The submission nominated placebo or standard care without carglumic acid. The ESC considered this was the appropriate comparator.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical studies

6.3 The submission was based on 12 non-randomised case report studies in which all patients were treated with carglumic acid in addition to conventional therapy for hyperammonaemia. A total of 58 patients with 71 reported episodes of hyperammonaemia secondary to IVA, MMA or PA were included in the 12 studies.

6.4 Details of the studies presented in the submission are provided in Table 1.

Table 1: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Case report studies		
Abacan 2013	Abacan M. & Boneh A. Use of carglumic acid in the treatment of hyperammonaemia during metabolic decompensation of patients with propionic acidaemia.	Molecular Genetics and Metabolism 2013; 109(4), 397-401.
Camozzi 2009	Camozzi C.R., Millson M., Smit M. & Salter J. Orphan Europe-Carbaglu® Retrospective Observational Study of Hyperammonaemia in OA Decompensation Episodes.	Clinical study report, 21 July 2009
Fiilippi 2010	Filippi L., Gozzini E., Fiorini P., Malvagia S., La Marca G. & Donati M.A. N-carbamylglutamate in emergency management of hyperammonemia in neonatal acute onset propionic and methylmalonic aciduria.	Neonatology 2010; 97(3), 286-290.
Gebhardt 2005	Gebhardt B., Dittrich S., Parbel S., Vlaho S., Matsika O. & Bohles H. N-Carbamylglutamate protects patients with decompensated propionic aciduria from hyperammonaemia.	Journal of Inherited Metabolic Disease 2005; 28(2), 241-244.
Gebhardt 2003	Gebhardt B., Vlaho S., Fischer D., Sewell A. & Böhles H. N-carbamylglutamate enhances ammonia detoxification in a patient with decompensated methylmalonic aciduria.	Molecular Genetics and Metabolism 2003, 79(4), 303-304.
Jones 2008	Jones S., Reed C.A., Vijay S., Walter J.H. & Morris A.A. N-carbamylglutamate for neonatal hyperammonaemia in propionic acidaemia.	Journal of inherited metabolic disease 2008; 31(Suppl 2), S219-222.
Kasapkara 2011	Kasapkara C.S., Ezgu F.S., Okur I., Tumer L., Biberoglu G. & Hasanoglu A. N-carbamylglutamate treatment for acute neonatal hyperammonemia in isovaleric acidemia.	European Journal of Pediatrics 2011, 170(6), 799-801.
Khan2013	Khan A., Casey R., Ferreira P. & Reeves M. Mut(0)-methylmalonic acidemia: Carglumic acid can help lower blood ammonia levels and allow for adequate protein intake.	Journal of Inherited Metabolic Disease 2013, 36(2), S184-S185.
Levesque 2010	Levesque S., Karalis A., Lambert M. & Russell L. Outcome of propionic acidemia treated at presentation with N-carbamylglutamate.	Molecular Genetics and Metabolism 2010, 99:3, 203.
Levrat 2008	Levrat V., Forest I., Fouilhoux A., Acquaviva C., Vianey-Saban C. & Guffon N. Carglumic acid: an additional therapy in the treatment of organic acidurias with hyperammonemia?	Orphanet journal of rare diseases 2008 , 3, 2.
Schwahn 2010	Schwahn B.C., Pieterse L., Bisset W.M., Galloway P.G. & Robinson P.H. Biochemical efficacy of N-carbamylglutamate in neonatal severe hyperammonaemia due to propionic acidaemia.	European Journal of Pediatrics 2010, 169:1, 133-134.
Soyucen 2010	Soyucen E., Demirci E. & Aydin A. 2010. Outpatient treatment of propionic acidemia-associated hyperammonemia with N-carbamoyl-L-glutamate in an infant.	Clinical Therapeutics, 2010 32:4, 710-713.

Source: Table B:6, pp32-33 of the submission

6.5 The key features of the case report studies are summarised in Table 2.

Table 2: Key features of the included evidence

Study	N (episodes)	Design, duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Carglumic acid plus conventional therapy						
Abacan 2013	3 (8)	RCR, 1-3 days	High	PA	Plasma Ammonia reduction	Yes
Camozzi 2009	39 (45)	RCR, 1-15 days	High	PA, MMA, IVA	Plasma Ammonia reduction	Yes
Fiilippi 2010	2 (2)	RCR, 10-29 days	High	PA, MMA	Plasma Ammonia reduction	Yes
Gebhardt 2005	2 (2)	RCR, 3 days	High	PA	Plasma Ammonia reduction	Yes
Gebhardt 2003	1 (1)	RCR, 4 days	High	MMA	Plasma Ammonia reduction	Yes
Jones 2008	1 (2)	RCR, 1-7 days	High	PA	Plasma Ammonia reduction	Yes
Kasapkara 2011	1 (1)	RCR, 10 days	High	IVA	Plasma Ammonia reduction	Yes
Khan2013	1 (1)	RCR, unknown	High	MMA	Plasma Ammonia reduction	Yes
Levesque 2010	3 (3)	RCR, 2-3 days	High	PA	Plasma Ammonia reduction	Yes
Levrat 2008	2 (2)	RCR, 3-4 days	High	PA, MMA	Plasma Ammonia reduction	Yes
Schwahn 2010	2 (3)	RCR, 1-2 days	High	PA	Plasma Ammonia reduction	Yes
Soyucen 2010	1 (1)	RCR, 4 days	High	PA	Plasma Ammonia reduction	Yes

RCR = Retrospective Case Report; PA = Propionic Acidaemia; MMA = Methylmalonic Acidaemia; IVA = Isovaleric Acidaemia
Source: compiled during the evaluation

6.6 Filippi 2010, Jones 2008, Kasapkara 2011, Khan 2013, Levesque 2010 and Schwahn 2010 also reported some patient relevant outcomes including developmental assessments and survival. However these outcomes were not formally quantified and were not used in the submission's clinical claim or the economic evaluation.

6.7 The PSCR noted that the rarity of the organic acidaemia conditions make the running of suitably powered randomised clinical trials very difficult. The ESC acknowledged the challenges regarding the availability of reliable data in the context of such a rare condition.

Comparative effectiveness

6.8 Given that only single arm case report studies have been identified, there were no comparative effectiveness outcomes reported by the submission. However, the submission presented the change in plasma ammonia levels and the number of cases with normalised ammonia levels after treatment, which included treatment with carglumic acid, summarised in Table 3.

Table 3: Results of reductions in ammonia levels across the indications reported in the studies

Type of acidaemia	Baseline ammonia in µmol/L	Ammonia after treatment in µmol/L	Difference in ammonia levels in µmol/L (%)	Normalised cases[1] n (%)
PA (n=40)	460	74	386 (83.9)	33 (82.5)
MMA (n=26)	327	67	260 (79.5)	23 (88.5)
IVA (n=5)	647	53	594 (91.8)	5 (100)
Total OA (n=71)	424	70	354 (83.5)	61 (85.9)[2]

[1] defined as plasma ammonia level ≤100 µmol/L in neonates and ≤50 µmol/L in children or adults
[2] estimated average time taken to reach normalisation from first dose of carglumic acid was 32.7 hours
PA = Propionic Acidaemia; MMA = Methylmalonic Acidaemia; IVA = Isovaleric Acidaemia; OA = Organic Acidaemias
Source: Table B:16, p103 and table B:20, p108 of the submission

6.9 The ESC considered that the risk of bias in the studies was very high due to the small number of patients, the large number of confounders and lack of control patients. The submission assumed that the decrease in ammonia levels was attributable solely to carglumic acid administration, which likely overestimated the

true ammonia level lowering effect of carglumic acid as there were a large number of concomitant therapies used to lower ammonia levels which the submission did not attempt to account or adjust for. Further, the evaluation considered it was unclear if it was appropriate to combine all the patients from the different studies and derive a mean ammonia level given the heterogeneity in the patients and the doses and types of therapies given to treat the hyperammonaemia episode.

6.10 The ESC considered that the claim that carglumic acid reduces ammonia levels was adequately supported while noting the difficulty in determining the true magnitude of the reduction attributable solely to carglumic acid.

6.11 Enns 2007 was a study which attempted to determine whether treatment with sodium phenylacetate and sodium benzoate reduced mortality due to acute hyperammonaemia due to urea-cycle disorders, as compared with historical data. Like the carglumic acid studies included in the submission, Enns 2007 reports the changes in ammonium levels observed in patients who received treatment similar to what the submission describes as the current treatment regimen with no carglumic acid. Of the neonates who survived, a median ammonium level at baseline of 374 µmol/L and 24 µmol/L at the end of treatment was observed. The median ammonium levels observed in the carglumic acid studies at baseline and end of treatment were 315 µmol/L and 59 µmol/L, respectively (where greater than 80% of all patients in the studies identified were neonates, though not all patients were neonates).

6.12 The ASIEM claimed that the use of carglumic acid has been beneficial in several Australian patients with PA in several episodes of metabolic decompensation, in some cases preventing the need for haemofiltration. However, the ASIEM noted that the beneficial effect of carglumic acid in MMA is less pronounced, but that the data around ammonia levels before and after treatment are limited.

Comparative harms

6.13 No comparative harms were reported by the submission. The only adverse event reported in the 12 studies identified was a case of strong, non-offensive and aromatic urinary odour. The lack of adverse events may be a result of the short follow up (no more than 29 days), the age of the patients in the studies being very young and unable to report possible subjective adverse events, and the patients being generally unwell to begin with.

6.14 The ASIEM claimed that carglumic acid is well tolerated by all patients at all ages.

Clinical claim

6.15 The submission described carglumic acid as having superior long-term efficacy when added to current standard of care (a low protein or protein-free diet, high calorie nutrition, arginine supplementation, ammonia scavengers and haemofiltration as rescue therapy), and is well tolerated with no reports of significant adverse effects to the drug. This claim is not adequately supported as:

- the level of evidence (case reports) did not allow for a superiority claim given the lack of information on the outcomes of patients in the absence of carglumic acid treatment;

- the "long term efficacy" of carglumic acid was not clearly defined (though assumed to be the absence of developmental delay or neurological damage and continual survival) and was not supported by the evidence, as the longest follow-up in the study was at 29 days of treatment, with only two out of the 58 patients having been observed beyond three years of age;
- there were many confounding factors with the evidence, including varying doses of carglumic acid administered, varying doses and types of concomitant therapies, different duration of treatment, different time elapsed since treatment initiation, and different peak levels of ammonia which were not accounted or adjusted for in the submission;
- the evidence presented focused on a surrogate outcome, plasma ammonia levels, which may not be correlated with patient relevant outcomes such as survival and developmental retardation as carglumic acid does not affect the levels of toxic metabolites (apart from ammonia) already accumulated in the body. The ESC noted that an assessment of decreased ammonia level, as a surrogate outcome for target clinical outcomes such as survival and development, was undertaken during the evaluation using the PBAC surrogate to finals outcome framework. The evaluation concluded that the relationship was unclear and subject to inherent bias; and
- the submission assumed that carglumic acid will be effective in the treatment of neonates, children and adults. However, only two patients (both reported by Camozzi 2009) were older than 10 years of age, with the mean age of all patients being less than one year in all studies. Noting the lack of data in adults, the ESC noted that it was unclear if patients would continue to have decompensation episodes as they get older.

6.16 Overall, given the level of evidence, the evaluation and the ESC considered it was reasonable to expect that treatment with carglumic acid along with current standard therapy (including a low protein or protein-free diet, high calorie nutrition, arginine supplementation, ammonia scavengers and/or haemofiltration as rescue therapy) will lead to a decrease in plasma ammonia levels in the short term, and carglumic acid is likely to have a reasonable safety profile. It is also known that carglumic acid will not decrease the levels of other toxic metabolites including methylmalonate, methylcitrate and propionyl-CoA, all of which contribute to the morbidity and mortality of the metabolic decompensation episode. The effect of carglumic acid on long term patient outcomes such as mortality and developmental retardation is unknown, and the comparative safety and effect of carglumic acid plus standard therapy versus standard therapy alone is also unknown.

6.17 The PBAC agreed with ESC that the submission did not demonstrate the comparative safety and efficacy of carglumic acid plus standard therapy versus standard therapy alone.

Economic analysis

6.18 The submission presented a simple cost-effectiveness analysis based on carglumic acid drug costs per episode (see Table 4). The results are summarised in Table 5.

Table 4: Summary of model structure and rationale

Component	Summary	Comment
Treatment duration	5 days	May not be appropriate to apply to all types of OA as a different duration of therapy is required by each patient group.
Time horizon	5 days in the model base case versus 1-29 days in studies	
Outcomes	Patients normalised; and One µmol/L reduction in mean ammonia.	These surrogate outcomes have not been formally linked to long-term clinically relevant outcomes.
Methods used to generate results	Study-based	The overall body of clinical evidence is of low quality, and it is difficult to determine the incremental safety and efficacy of carglumic acid as there are many confounding factors in the case reports.
Age groups and distribution	Baby: 50% Child: 50%	Differs to the study population (82% babies, 15% children and 3% adults).
Age groups and weight	Baby (6 months): 7.8kg Child (10 years): 32.5 kg	The "child" group is actually 1-10 years (not 1-18 years) from the study population.

Abbreviations: OA = organic acidaemias. Source: compiled during the evaluation

Table 5: Results of the economic evaluation (total organic acidaemias)

Component	Carglumic acid	Standard care	Increment
Costs	$[redacted]	$0	$[redacted]
patient normalised – total OA	86%	0	86%
Incremental cost/extra patient normalised			**$[redacted]**
Costs	$[redacted]	$0	$[redacted]
reduction in mean ammonia (µmol/L) – total OA	354	0	354
Incremental cost/one µmol/L reduction in mean ammonia			**$[redacted]**

Abbreviations: OA = organic acidaemias. Source: Tables D:7-D:8, p127 of the submission

The redacted table above shows that the incremental cost per extra patient normalised and for one µmol/L reduction in mean ammonia were less than $15,000.

6.19 The cost-effectiveness ratios estimated in the submission were largely uninformative due to the following issues:

- the submission assumed that the reduction in ammonia levels was solely attributable to carglumic acid, where patients in the studies were treated with a variety of additional therapies;
- these surrogate outcomes were not formally linked to clinically relevant outcomes such as life years gained and a review of the relationship undertaken during the evaluation found it was unclear and subject to inherent bias; and
- the results were unreliable due to uncertainty regarding carglumic acid costs as there was a wide variation around average patient weight and treatment duration.

6.20 The ESC considered that if any patients were being treated in an outpatient setting, and therefore would be eligible to access the drug through the PBS, it would likely be older children as infants are more likely to be treated in an inpatient setting. This reasoning is based on a study by Evans et al (2007), which found that better survival was associated with the age of infants when they experienced their first decompensation episode, (that is, older infants were more likely to survive). Therefore if older infants and children are more likely to survive perhaps they are more likely to be treated as outpatients than infants. Accordingly, if older children are more likely to be treated on an outpatient basis then this is likely to result in higher average drug costs (in line with the higher average weight) for the PBS population, compared with patients that receive the drug while admitted to hospital. However the

proportion of infants versus older children and adults likely to be treated as outpatients is currently unknown, and it is was not clear how the submission had proposed the 50:50 distribution between infants and children.

6.21 The results of the sensitivity analyses indicated that the model was most sensitive to the average weight based on the assumed age distribution of the treated population, and the treatment duration for carglumic acid.

Drug cost/patient/course: $[redacted]

6.22 $[redacted] per patient per course per organic acidaemia decompensation episode, assuming an average patient weight of 20.15 kg, treatment duration of five days and no wastage.

Estimated PBS usage & financial implications

6.23 This submission was not considered by DUSC. The submission reasonably used an epidemiological approach based on the incidence of organic acidaemia decompensation episodes in Victoria, to estimate the extent of use and financial implications of the requested listing for carglumic acid, summarised in Table 6.

6.24 The submission's estimate of the number of episodes per year likely to be treated is based on the number of organic acidaemia decompensation episodes in Victoria from personal communication with a clinician, assumed to be correlated with population size in Australia. Whether this is an over- or under-estimate was unknown because the number of episodes could not be independently verified.

6.25 The ESC noted that it was unclear if there are any patients who are not currently accessing treatment who need it or how many may be paying privately for such treatment. The PSCR claimed that carglumic acid is funded by public hospitals and patients which results in a financial burden to both groups as well as under-use due to the cost. The ESC noted that this barrier to access for patients was not substantiated in either the submission or the PSCR and was unlikely to be the case for the majority of patients who would be treated while admitted to a public hospital.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Bottles[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

[a] Assuming 13.04 bottles (200mg tablets x 5) per patient (no wastage scenario) as estimated by the submission.
Source: Table E:3, p 134 of the submission

6.26 The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million.

6.27 Key sensitivity analyses are provided in Table 7.

Table 7: Key sensitivity analysis of the total net cost to the PBS/RPBS of listing carglumic acid

	Year 1	Year 2	Year 3	Year 4	Year 5
Base Case (duration=5 days; weight=20.15kg)	$	$	$	$	$
Duration of treatment with carglumic acid: 7 days[a]	$	$	$	$	$
Duration of treatment with carglumic acid: 3 days	$	$	$	$	$
20% increase in average weight	$	$	$	$	$
Duration of treatment with carglumic acid: 7 days [a] AND 20% increase in average weight	$	$	$	$	$

[a] In the submission's analysis in Table E.4 (p139), the submission erroneously did not multiply the estimated increase in use of 259 mg/kg (from the increase in treatment duration to 7 days) by the average weight (kg) per patient, hence under-estimating costs.

6.28 The estimates were most sensitive to the duration of treatment with carglumic acid and average weight based on the age distribution.

Financial Management – Risk Sharing Arrangements

6.29 The submission stated that the sponsor was willing to undertake a risk sharing arrangement. No further details were provided.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC rejected the request to list carglumic acid on the PBS for the treatment of hyperammonaemia on the basis that it considered that the PBS was not the appropriate mechanism for dispensing carglumic acid, in light of advice provided by the ASIEM.

7.2 The PBAC noted the ASIEM advice that carglumic acid has only been used in the setting of hospital admission, and considered that the provision of carglumic acid to neonates and older children would constitute routine care provided by hospitals in the context of acute decompensation episodes. In this regard, the PBAC considered that there was no unmet clinical need to be addressed through listing carglumic acid on the PBS.

7.3 The PBAC noted that the submission did not provide evidence to support the sponsor's assertions that carglumic acid is currently being used in an outpatient setting, and that cost was a barrier to accessing treatment.

7.4 The PBAC agreed that standard care without carglumic acid was the appropriate comparator.

7.5 The PBAC noted that the available evidence for carglumic acid for this indication was limited to non-randomised case report studies with no comparator arm and very short follow-up periods. However, the PBAC noted the challenges regarding availability of reliable data given the rarity of the condition.

7.6 The PBAC considered it reasonable to expect that treatment with carglumic acid, along with current standard therapy, would lead to a decrease in plasma ammonia levels in the short term and carglumic acid is likely to have a reasonable safety profile. However the effect of carglumic acid on long-term patient outcomes, such as mortality and developmental retardation was unknown. Further, the PBAC noted that

the comparative safety and efficacy of carglumic acid plus standard therapy versus standard therapy alone was also unknown.

7.7 The PBAC noted that the cost effectiveness analysis provided in the submission was uninformative due to the issues raised by the ESC (see paragraph 6.19).

7.8 The PBAC noted the challenges in identifying the patient population for this indication and that the estimated number of patients could not be independently verified.

7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.