PUBLIC SUMMARY DOCUMENT

Product: BETAINE, 1 g/g oral liquid: powder for, 180 g, Cystadane®
Sponsor: Emerge Health Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The submission requested an Authority Required General Schedule listing for the treatment of patients with homocystinuria.

2. Background

This submission had not previously been considered by the PBAC.

3. Registration Status

Betaine was TGA registered on 1 October 1996 as an adjunct in the treatment of homocystinuria.

4. Listing Requested and PBAC's View

Authority required
Adjunct treatment for homocystinuria.

The submission requested listing on a cost effectiveness basis compared with standard care.

The PBAC considered it would be appropriate to ensure that prescribing of betaine was undertaken in consultation with a metabolic physician.

The PBAC considered that a maximum quantity of 1 bottle would be sufficient for one month's supply for most patients, but acknowledged that some patients would require higher doses and agreed that physicians should be able to apply for a maximum quantity of up to 3 bottles per Authority prescription.

5. Clinical Place for the Proposed Therapy

Homocystinuria is a metabolic condition caused by rare inherited disorders of amino acid metabolism. Homocystinuria is characterised by excessive homocysteine levels with accompanying abnormalities in methionine and cysteine levels.

Untreated homocystinuria is associated with premature death, vascular disease/thromboembolic events, intellectual disability, ocular symptoms, skeletal symptoms and seizures.

Betaine anhydrous acts a methyl donor that remethylates homocysteine to methionine and therefore reduces homocysteine levels. Based on the limited available information it appears that patients with pyridoxine-responsive homocystinuria are primarily managed with

pyridoxine, folate and cobalamin with or without a protein-restricted diet. Patients non-responsive to pyridoxine are primarily managed with a methionine-restricted diet in combination with pyridoxine, folate, cobalamin and cysteine supplements.

The proposed place in therapy for betaine was inconsistently described between the requested listing (all homocystinuria patients), eligibility criteria (pyridoxine non-responsive patients) and clinical management algorithm (symptomatic patients).

6. Comparator

The submission nominated standard care without betaine as the comparator. The PBAC considered that this was appropriate.

7. Clinical Trials

No head-to-head trials comparing treatment with betaine with standard care without betaine were presented in the submission.

The submission presented five non-randomised studies reporting changes in biochemical parameters and/or clinical outcomes associated with betaine therapy (Singh et al 2004, Walter et al 1998, Wilcken et al 1983, Wilcken et al 1985, Wilcken et al 1997).

The submission also presented, as supportive evidence, an historical, multinational case control study comparing vascular outcome in treated versus untreated patients with homocystinuria (Yap et al 2001, Yap et al 2003).

The PBAC noted the evaluation examined the relationship between the surrogate biochemical parameter (plasma homocysteine) and clinically relevant outcomes (vascular outcomes). There were no data presented on other clinical outcomes. The PBAC considered that the association of reduction in homocysteine plasma levels and vascular events was plausible but that the evidence supporting the link was not strong.

The table below summarises the clinical data presented in the submission.

Trials and associated reports presented in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Key studies		
Singh (2004)	Singh et al (2004). Cystathionine B-synthase deficiency: Effect of betaine supplementation after methionine restriction in B6 non-responsive homocystinuria	Genetics in Medicine 6: 90-95
Walter (1998)	Walter et al (1998). Strategies for the treatment of cystathionine beta-synthase deficiency: the experience of the Willink Biochemical Genetics Unit over the past 30 years	European Journal of Pediatrics 157: S71-S76
Wilcken (1983)	Wilcken et al (1983). Homocystinuria –the effects of betaine in the treatment of patients not responsive to pyridoxine	New England Journal of Medicine 309:448-453
Wilcken (1985)	Wilcken et al (1985). Homocystinuria due to cystathionine beta-synthase deficiency – the	Metabolism 35:1115-1121

Trial ID/First author	Protocol title/ Publication title	Publication citation
	effects of betaine treatment in pyridoxine-responsive patients	
Wilcken (1997)	Wilcken et al (1997). The natural history of vascular disease in homocystinuria and the effects of treatment	Journal of Inherited Metabolic Disease 20:295-300
Supportive studies		
Yap (2001/2003)	Yap et al (2001). Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically	Arteriosclerosis Thrombosis and Vascular Biology21:2080-2085
	Yap (2003). Classical homocystinuria: Vascular risk and its prevention.	Journal of Inherited Metabolic Disease 26:259-265

The PBAC noted consumer input from the Australasian Society for Inborn Errors of Metabolism (ASIEM). ASIEM's input highlighted the effectiveness of betaine in treating homocysteinurias, and the difficulty faced by patients in obtaining betaine at a reasonable price in the absence of PBS listing.

The PBAC noted that the sponsor did not request a hearing.

8. Results of Trials

The table below summarises individual study results reporting homocysteine levels with and without betaine treatment.

Mean homocysteine levels with and without betaine

Study (N, duration)	Mean Hcy levels (µmol/L)		Absolute change (µmol/L)	Relative change (%)
	Without betaine	With betaine		
Singh (2004) (N = 5, 3-6 months)	70.28	22.90	-47.38	-70.45
Walter (1998) (N = 13, 2-30 years)[a]	35.00	33.00	-2.00	-5.71
Wilcken (1983) (N = 11, 10 months)	139.09	34.00	-105.09	-72.28
Methionine challenge study (Wilcken 1985) (N = 6, 3 months)	0 hr: 8.7 4 hr: 46.6 8 hr: 50.9 12 hr: 47.6 24 hr: 60.9	0 hr: 6.4 4 hr: 16.6 8 hr: 22.7 12 hr: 23.4 24 hr: 20.8	0 hr: -2.28 4 hr: -29.95 8 hr: -28.20 12 hr: -24.22 24 hr: -40.05	0 hr: -24.48 4 hr: -63.23 8 hr: -53.81 12 hr: -51.74 24 hr: -68.84
Pooled analysis of individual patient data Singh (2004), Walter (1998), Wilcken (1983) and Wilcken (1985)				
Pooled data (N = 35)	74.12	29.3	-44.82	-44.75

Abbreviations: Hcy, homocysteine

[a] Only included pyridoxine non-responsive patients who were treated with betaine;

The submission claimed that treatment with betaine was associated with a substantial reduction in homocysteine levels compared to prior measurements without betaine. The changes in homocysteine levels associated with betaine therapy were not consistent between studies. The study results ranged from no effect (Walter et al 1998) to an average reduction of approximately 70% from baseline (Singh et al 2004, Wilcken et al 1983). For comparison,

both the ROCH patient registry and the approved Product Information noted that betaine usually reduces homocysteine levels by approximately 20-30% from baseline.

The table below presents a comparison of vascular outcomes between an Australian cohort of treated homocystinuria patients and an historical international cohort of untreated homocystinuria patients (Wilcken et al 1997).

Vascular outcomes in treated (Australian cohort) versus untreated (historical control) patients

Population Wilcken (1997)	Patients (subject years)	Mean Hcy levels µmol/L	Vascular events		
			Observed	Predicted[a]	RR (95% CI)
All patients	32 (539)	NR	2	21	0.09 (0.02, 0.38)
Pyridoxine responsive patients (not treated with betaine)	17 (281)	< 20	2	11	0.17 (0.04, 0.80)
Pyridoxine non-responsive patients (treated with betaine)	15 (258)	33	0	10	NR p = 0.005

Abbreviations: CI, confidence interval; Hcy, homocysteine; NR, not reported; RR, relative risk
[a] Based on the historical control group

The submission claimed that the vascular event rate in pyridoxine non-responsive patients treated with betaine (0/15, 0%) was lower than pyridoxine-responsive patients not treated with betaine (2/17, 11.8%). Similarly, the submission claimed that the risk of death in pyridoxine non-responsive patients treated with betaine (0/15, 0%) was lower than pyridoxine responsive patients not treated with betaine (1/17, 5.9%).

The PBAC considered that this study demonstrated that patients receiving homocysteine-lowering treatments had a lower risk of vascular events compared to an untreated historical control (RR 0.09; 95% CI 0.02, 0.38). While the magnitude of benefit may be overestimated due to the limitations of the study design (historical case control), the PBAC considered it reasonable to expect some reduction in vascular event risk with treatment. The PBAC considered this study to be the most informative in terms of comparative efficacy of betaine in the treatment of homocystinuria.

The PBAC noted that treatment with betaine was associated with an increased incidence of nausea, diarrhoea and gastrointestinal effects.

Betaine treatment has also been associated with cases of cerebral oedema due to hypermethionaemia. The PBAC noted in the periodic safety update report that pharmacovigilance activities will continue to monitor the potential risk of cerebral oedema due to hypermethioninaemia associated with betaine therapy, and that the submission estimated the incidence of cerebral oedema at approximately 1 case per 1,584 patient years treated with betaine (based on 6 reported cases and a cumulative estimated exposure of 9,506 patient years).

The PBAC noted that no additional safety concerns were identified for the period March 2012 to February 2013 in the Periodic Safety Update Report.

9. Clinical Claim

The submission described betaine as superior in terms of comparative effectiveness compared to standard care. The PBAC considered that this was reasonable; however, the magnitude of the clinical benefit was difficult to accurately quantify. The PBAC noted the association between homocysteine plasma concentrations and vascular outcomes.

The PBAC considered that the reduction in the number of vascular events from predicted shown in the Wilcken et al (1997) study was the most clinically relevant outcome for this patient population. The PBAC believed that this study supported the submission's claim of efficacy.

The PBAC noted that the submission did not make a comparative safety claim. The submission did note that betaine was generally well-tolerated. The PBAC considered that this was reasonable.

10. Economic Analysis

The submission presented a cost effectiveness analysis based on the annual cost of betaine and the pooled reduction in homocysteine levels from the included studies.
Treatment with betaine was associated with an incremental cost of less than $2,000 per 1 µmol/L reduction in homocysteine levels compared to standard medical management without betaine. This equated to an incremental cost of less than $10,000 per 5 µmol/L reduction in homocysteine levels. The submission claimed that this reduction may be associated with an improvement in cardiovascular risk.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

The PBAC considered that the estimates of utilisation and financial cost were highly uncertain due to assumptions regarding the prevalence of homocystinuria, uptake rates, patient adherence and average dose of betaine. The PBAC considered it would be appropriate to manage the utilisation of betaine with a risk share arrangement based on a cap on the number of patients, using the patient numbers presented in the submission.

12. PBAC Outcome

The PBAC recommended the listing for betaine as an Authority Required benefit for the adjunct treatment of homocystinuria, in consultation with a metabolic physician on the basis of improved vascular outcomes over standard care without betaine.

The PBAC was satisfied that betaine provides, for some patients, a significant improvement in efficacy over standard care.

The PBAC noted that homocystinuria is a rare disease for which there is a high need for new treatments.

The PBAC was satisfied that betaine provides, for some patients, a significant reduction in the risk of a vascular event, as well as reduced serum levels of homocysteine.

The PBAC acknowledged the difficulties associated in the collection of data in rare conditions such as homocystinuria.

The PBAC considered that the reduction in the number of vascular events from predicted shown in the Wilcken et al (1997) study was the most clinically relevant outcome for this patient population. The PBAC considered that this study supported the submission's claim of comparative effectiveness.

The PBAC considered that it was appropriate that a risk share arrangement is implemented to manage the uncertainty around the utilisation and total financial cost. This risk share arrangement should include a cap on patient numbers, using the estimates provided in the submission.

The PBAC noted that its recommendation was in the context of a small patient population with a high unmet clinical need, and a modest overall likely financial impact to the PBS.

The PBAC noted the advice received from the Australasian Society for Inborn Errors of Metabolism. This advice supported the use of betaine in the treatment of all forms of homocystinuria, and noted equity of access issues in the absence of a PBS listing.

The PBAC advised the Minister that under Section 101 3BA of the *National Health Act*, betaine should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

Outcome:
Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
BETAINE ANHYDROUS 1 g/g Powder, 180 g bottle	1	5	Cystadane	Emerge Health

Condition:	Homocystinuria
Restriction:	Authority Required
Clinical criteria:	The treatment must be as adjunctive therapy to current standard care.
Treatment criteria:	The condition must be treated by or in consultation with a metabolic physician
Administrative advice	The name of the specialist must be included in the authority application.

13. 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.

14. Sponsor's Comment

The sponsor appreciates the rapid and positive review of the evidence and subsequent positive recommendation for listing of betaine. This listing will provide a positive benefit for patients in Australia.