Scottish Medicines Consortium

Re-Submission

betaine anhydrous oral powder (Cystadane®) No. (407/07)
Orphan Europe (UK) Limited

06 February 2009

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

betaine anhydrous (Cystadane®) is not recommended for use within NHS Scotland as adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (cbl).

Clinical efficacy data for betaine anhydrous are limited.

The manufacturer did not present a sufficiently robust economic evaluation to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Adjunctive treatment of homocystinuria, involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (cbl). Betaine anhydrous should be used as supplement to other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), folate and a specific diet.

Dosing information

In adult and paediatric patients over 10 years of age, 6g per day administered orally in divided doses of 3g twice daily. Dose titration may be preferable in paediatric patients. In paediatric patients less than 10 years of age, the usual effective dose regimen is 100mg/kg/day given in two divided doses. Increasing the frequency above twice daily and/or the dose above 150mg/kg/day does not improve the homocysteine-lowering effect.

Betaine anhydrous treatment should be supervised by a physician experienced in the treatment of patients with homocystinuria.

Product availability date

28 March 2007. This product has orphan drug status.

Summary of evidence on comparative efficacy

Homocystinuria is an inherited disorder of the metabolism of the amino acid methionine leading to accumulation of homocysteine in the blood and urine. This is due to a dysfunction in one of the metabolic pathways responsible for transulfuration and remethylation of homocysteine. Homocystinuria is a serious life-long disease and is associated with a high morbidity and mortality. The major clinical manifestations include mental retardation, dislocation of the optic lens (ectopia lentis), skeletal abnormalities and a tendency to thromboembolic episodes.

No data are available from systematic efficacy studies of betaine anhydrous (subsequently referred to as betaine) in the treatment of homocystinuria. For the European regulatory submission, the review of pharmacodynamic data for betaine indicated that it lowers plasma total homocysteine concentrations in healthy subjects and patients with homocystinuria (homocysteine plasma concentrations are generally accepted as a surrogate marker for the severity of disease) and it improves metabolic abnormalities in the central nervous compartment of patients with homocystinuria. Clinical efficacy data were based on 202 reports retrieved from literature searches. Verified data were available for 140 patients, in which individual biochemical or clinical features as well as dose and duration of betaine therapy, and pre-existing or concomitant therapies were documented. The European Medicines Agency's (EMEA) European Public Assessment Report (EPAR) notes that the data presented showing biochemical efficacy and the associated improvements regarding the various disease symptoms after betaine therapy compared with historical data of untreated patients provided sufficient evidence of betaine's effectiveness. However, limited referenced data were included in the submission to the Scottish Medicines Consortium (SMC) to enable assessment of this effectiveness.

With regard to disease symptoms, data on neurological, ophthalmologic and skeletal features are limited and it is difficult to draw meaningful conclusions. Vascular outcomes were analysed and effectiveness of treatment in reducing vascular risk was evaluated in a multi-centre observational study, including 158 CBS deficient patients with plasma total

homocysteine levels >150µm/L (44% vitamin B6-responders), by comparison of actual to predicted number of vascular events, using historical controls from a study of 629 patients with CBS deficiency who did not receive betaine. In the multi-centre observational study patients received combination therapy that included dietary methionine restriction and treatment with vitamin B6, folate, vitamin B12 (if required) and betaine. Patients were followed up with treatment for a mean duration of 17.9 years (2822 patient years of treatment). As one vascular event per 25 years was expected based on the historical data, the predicted number of vascular events during 2822 patient-years was at least 112 if patients remained untreated. Instead only 17 vascular events occurred in 12 patients who were undergoing treatment (relative risk 0.09, 95% Confidence Intervals: 0.036 to 0.228). Statistical analyses were repeated using only the first vascular event in each patient and the results were identical for all vascular events. These events occurred at a mean age of 42.5 years of age (range 18 to 67 years). There were five deaths resulting from vascular events.

A further study, involving 15 pyridoxine-non-responsive patients, demonstrated that following supplementation with betaine at 6g to 9g per day, plasma total free homocysteine levels decreased by an average of 74% and there were no vascular events during a total of 258 patient years, compared to at least 10 expected events.

Summary of evidence on comparative safety

Safety data from controlled studies are sparse. The analysis of betaine's safety in this resubmission was based on data published in the literature in addition to solicited reports obtained in Europe by Orphan Europe and a US survey and post marketing surveillance programme in the US undertaken by Orphan Medical.

The majority of side effects reported during treatment with betaine are mild and mainly related to the gastrointestinal system (diarrhoea, stomach discomfort, nausea and vomiting).

The EPAR for betaine notes that the occurrence of a limited number of potentially life-threatening cases of cerebral oedema whilst receiving standard doses of betaine raises concern. In this regard special attention should be paid in patients with poor dietary control of methionine; plasma methionine concentrations should be monitored at the start of treatment and periodically thereafter, especially in patients with CBS-deficiency receiving betaine.

Summary of clinical effectiveness issues

There is currently no treatment to correct the basic genetic causes of homocystinuria. The aim of treatment is to normalise homocysteine levels by several methods including boosting residual enzyme activity with vitamin B6, vitamin B12 and folates, reducing load on the metabolic pathway affected with low-methionine diet (CBS deficiency), supplementation with the deficient products downstream of the enzyme abnormality (cysteine for CBS deficiency and methionine for impaired remethylation) and using an alternative pathway to eliminate the toxic substrate. The latter approach involves the use of betaine, which remethylates homocysteine to methionine.

Clinical data to demonstrate the effectiveness of betaine in patients with homocystinuria are limited and consist of a number of case studies that are observational and uncontrolled and likely to be subject to selection, performance and publication bias. Clinical efficacy data considered in the European regulatory submission was based on data from a literature search. The EPAR notes that as a variety of doses and co-treatments have been used in this

literature search, several forms of bias might have influenced the results. As a consequence, the clinical efficacy of betaine treatment is more difficult to assess than the biochemical efficacy. Nevertheless, it is acknowledged that further clinical studies are unlikely to improve the evidence base due to the heterogeneous patient population in question.

It is likely that due to the multiple treatment strategies used (dietary, pharmaceutical, supportive) in patients with homocystinuria, there may be an element of overestimation in the clinical effects of betaine treatment. However, with the data presented it is difficult to determine the benefits of betaine plus standard therapies over standard therapies alone. Nevertheless, clinical experts have confirmed that betaine is part of the standard treatment plan for homocystinuria in Scotland and it has been used for many years on a named patient basis as an adjunctive therapy. There is therefore experience of use in practice with retrospective reports of efficacy and few reported safety concerns.

As the available clinical data do not allow correlation of dosage and clinical efficacy of betaine, the dosage used in practice is not critical. However, good practice with the use of an agent where limited clinical data are available would suggest that patients receiving betaine should have biochemical monitoring performed on a regular basis by a physician experienced in metabolic disorders.

Summary of comparative health economic evidence

The manufacturer presented a simplistic number needed to treat (NNT) analysis for the avoidance of one death. The anticipated survival for that death avoided was then projected to arrive at a cost per life year gained.

The annual death rate without betaine treatment was estimated to be 0.50% while with betaine treatment was estimated to be 0.15% to give a net effect of 0.35%. Given an annual net drug cost based upon 6g per day of betaine of £3,540, this translated into a cost per death avoided of approximately £1 million. The additional life expectancy was projected as being from the age of 30 to the age of 42, or a 12 year survival gain, hence a cost per life year of £80k.

Weaknesses included:

- the relative clinical effectiveness apparently being largely by assumption;
- an unusual modelling approach using a NNT per death avoided rather than the cost-utility approach used in the previous submission to SMC;
- ignoring the costs of the therapy betaine would be adjunctive to;
- ignoring any cost and quality of life effects from the complications of CBS, and of the impact of betaine treatment upon these;
- annual betaine drug costs being underestimated as they were based upon 12 times 28 days at the lowest adult dose of 6g per day;
- the costs of monitoring for and treatment of any cerebral oedema were not included.

The manufacturer provided an additional analysis, using a different approach and different data inputs, to address some of these concerns. Using a cohort of 100 patients over a 10 year period the manufacturer estimated that serious events or death would be avoided in 21 patients at a net cost of £9.67 million. This was based on a 9g daily dose of betaine and £220,000 of saved costs from avoiding serious events. The manufacturer therefore estimated an annual cost per patient who benefited of £46,580. While addressing some of the concerns with the original analysis, this simple analysis also had a number of limitations.

Given these issues, the manufacturer did not present a sufficiently robust economic evaluation to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Children Living with Inherited Metabolic Diseases. (CLIMB)

Additional information: guidelines and protocols

There are no relevant guidelines or protocols available for the treatment of homocystinuria or the use of betaine for this condition. The Online Mendelian Inheritance in Man (OMIM) database provides relevant information on the genetics of homocystinuria with limited information on clinical and biochemical features, pathogenesis and clinical management.

Additional information: comparators

There are no licensed comparator products available. Betaine (as monohydrate) and betaine anhydrous (Cystadane) have been used for many years on a named-patient basis as an adjunct to dietary restrictions and vitamin therapy for the treatment of homocystinuria in neonates, infants and children of different age groups.

Cost of relevant comparators

The cost of betaine anhydrous (Cystadane) was obtained from eVadis on 11 November 2008. For patients younger than 10 years of age the annual cost of treatment (calculated over 365 days) is £1,910 (based on a dose of 100mg/kg/day in a 30kg child). For patients 10 years of age and older, the annual cost of treatment is £3,820 (based on a dose of 3g twice daily).

Additional information: budget impact

The manufacturer estimated that 25 to 30 patients would receive treatment with betaine per year . Dosage would range between 6g per day and 9g per day on average yielding a gross drug cost of between £97k and £174k in year 1, rising to between £98k and £186k by year 5. There was no net drug cost estimate, due to betaine being adjunctive therapy. These figures do not take into account the costs of the unlicensed betaine anhydrous product that is currently used on a named patient basis and is significantly less expensive.

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 16 January 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Mudd HS, Skovby F, Levy HL et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet 1985;37(1):1-31

Yap S, Boers GHJ, Wilcken B et al. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: a multicenter observational study. Arterioscler Thromb Vasc Biol 2001;21(12):2080-5

Wilcken DEL, Wilcken B. The long-term outcome in homocystinuria. In: I. Biochemistry and genetic studies: p51 to 56. Homocysteine metabolism: from basic science to clinical medicine. Edited by Graham I, Refsum H, Rosenberg IH, Ueland PM. Kluwer Academic Publishers 1997

The European Medicines Agency (EMEA). European Public Assessment Report for betaine anhydrous (Cystadane®), 13/02/2008 EMEA-H-C-678. www.emea.europa.eu