Resubmission

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

09 July 2010

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 second resubmission

betaine anhydrous (Cystadane®) is accepted for restricted use within NHS Scotland.

Indication under review: adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylene-tetrahydrofolate reductase (MTHFR) or cobalamin cofactor metabolism (cbl).

SMC restriction: patients who are not responsive to vitamin B_6 treatment.

Limited clinical data confirmed the effectiveness of betaine anhydrous in homocystinuria, There remains some uncertainty about the cost-effectiveness of betaine anhydrous even in the restricted patient group described above, but given the orphan nature of the condition the economic case for use was accepted.

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

March 2007. Betaine anhydrous (Cystadane) was granted orphan drug status in July 2001.

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.

The submitting company has presented the health economics for this resubmission in a subset of the licensed population i.e. those patients who are not responsive to vitamin B_6 treatment.

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 lowered plasma total homocysteine concentrations in healthy subjects and in patients with homocystinuria (homocysteine plasma concentrations are generally accepted as a surrogate marker for the severity of disease) and it improved 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 (EMA) European Public Assessment Report (EPAR) noted 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 the effectiveness of betaine.

Information about disease symptoms, such as data on neurological, ophthalmologic and skeletal features is limited. 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 B_6-responders), by comparison of actual to predicted number of vascular events, using historical controls from a study of 629 patients with CBS deficiency who had not received betaine. In the multi-centre observational study patients received combination therapy that included dietary methionine restriction and treatment with vitamin B_6, folate, vitamin B_{12} (if required) and betaine. Patients were followed up for a mean duration of 17.9 years (2,822 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 2,822 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). Twelve vascular events were reported in eight vitamin B_6 responsive patients and five events in four vitamin B_6 non-responsive patients but there was no analysis compared to historical controls according to vitamin B_6 responsiveness. 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

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 European Product Assessment Report (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 B_6, vitamin B_{12} 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. Clinical efficacy data considered in the European regulatory submission were based on data from a literature search. The EPAR noted that as a variety of doses and co-treatments had 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. 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.

The submitting company has presented the health economics for this resubmission in patients who are not responsive to vitamin B_6 treatment. These patients have a more severe phenotype of the disorder.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis of betaine 6g per day plus standard care compared to standard care alone for the subset of patients who are non-responsive to vitamin B_6 treatment. This used a relatively simple cost utility decision tree modelling framework over a sixty-year time horizon to estimate the rates of vascular events for standard care and betaine adjunctive to standard care. While the majority of vascular events were modelled as being non-fatal, these were associated with quality of life and cost impacts.

The main estimate of clinical effectiveness related to the relative risk of vascular events of 0.09 for betaine plus standard care as compared to standard care, as derived from the observational study summarised in the comparative efficacy section.

The utility for patients not experiencing a vascular event was drawn from a survey among three Scottish experts. The utility values for vascular events were taken from the literature and this quality of life impact was assumed to apply for the remainder of the patient's lifetime.

This resulted in an estimated survival of 59.7 years for betaine plus standard care as compared to 58.3 years for standard care alone. The incremental quality adjusted life year (QALY) gain was 1.4 QALYs and the incremental cost was £70,883 to give a cost effectiveness estimate of £52,621 per QALY.

Results were sensitive to limiting the quality of life impact of vascular events to only one year, the utilities values used, discount rates, dose of betaine assumed and to a lesser degree the relative risk of a vascular event. However, the cost-effectiveness estimate did not take account of other potential benefits of betaine treatment such as reduced mental retardation or skeletal effects, which would lower the cost per QALY were they included.

While the base case cost-effectiveness ratio is comparatively high, the economic case was considered demonstrated given that the product has orphan status and provides a licensed alternative to an unlicensed product in current use.

Summary of patient and public involvement

A Patient Interest Group submission was received from 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 28 April 2010. For patients under 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 around 84 patients have homocystinuria with between 30% (25 patients) and 35% (30 patients) receiving betaine. The manufacturer estimated that the daily dose would range between 6g and 9g on average. This yielded 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 any unlicensed betaine anhydrous used on a named patient basis.

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 17 June 2010.

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. 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.

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

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