Scottish Medicines Consortium

betaine anhydrous oral powder (Cystadane®) No (407/07)

Orphan Europe

7 September 2007

The Scottish Medicines Consortium 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 full submission

betaine anhydrous (Cystadane®) is not recommended for use within NHS Scotland as adjunctive treatment of homocystinuria in line with the manufacturer's licence.

The manufacturer did not provide sufficient clinical data to demonstrate efficacy.

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.

Product availability date

28 March 2007.

Summary of evidence on comparative efficacy

Homocystinuria is a rare hereditary disease affecting the metabolism of methionine; it has serious effects on the central nervous system, cardiovascular system and bone. Symptoms can include mental retardation, dislocation of the optic lens, seizures, psychiatric disturbances, osteoporosis and thromboembolic complications. If left untreated, 25% of homocystinuria patients die before the age of 30. Betaine anhydrous (subsequently referred to as betaine) has orphan drug status for the treatment of homocystinuria. It acts by remethylation of homocysteine to methionine, thereby reducing plasma levels of homocysteine.

The European Medicines Agency's (EMEA's) European Patient Advice Report (EPAR) notes that the data presented for the European regulatory submission 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 data were included in the submission to the Scottish Medicines Consortium (SMC) to enable assessment of this effectiveness.

No data are available from systematic efficacy studies of 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. These data were not included in the manufacturer's submission to SMC.

With regard to disease symptoms, data on improvement in neurological symptoms are 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 (44% vitamin B6-responders), by comparison of actual to predicted number of vascular events, using historical controls from a study of 629 untreated patients with CBS deficiency. 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 1 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, $p< 0.0001$). 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 5 deaths resulting from vascular events.

A further study, involving 15 pyridoxine-non-responsive patients who had at least one vascular event, demonstrated that following supplementation with betaine at 6 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.

Summary of evidence on comparative safety

Safety data from controlled trials are sparse. In a multi-centre observational study including 170 CBS deficient patients who had a total of 825 patient-years of betaine treatment, there were no reports of significant side effects. The longest period of betaine treatment in this group at the time of reporting was 17 years.

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 EMEA's EPAR notes that the occurrence of a limited number of potentially life-threatening cases of cerebral oedema whilst receiving the usual dose of betaine raises concern. In this regard special attention should be paid in patients with poor dietary control of methionine and methionine plasma 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. Consequently, therapy is directed at correcting the biochemical abnormalities of these disorders. Betaine has 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. As such, despite the lack of robust clinical evidence, there is experience of use in practice with retrospective reports of efficacy and few reported safety concerns.

Clinical data to demonstrate the effectiveness of betaine in patients with homocystinuria are limited. Further studies are unlikely to improve the evidence base due to the heterogeneous patient population in question. Clinical efficacy data considered in the European regulatory submission was based on data from a literature search. Specific details of the results of this literature search were not included in the manufacturer's submission . The EMEA's 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.

Furthermore, it is likely that due to the multiple nature of therapy (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.

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 there are limited clinical data available would suggest that patients receiving betaine should have biochemical monitoring performed on a regular basis by a physician experienced in metabolic disorders.

It should be noted that the data considered in this submission relate to patients with CBS deficiency homocystinuria, which is the most common form of the disease. However betaine is licensed for use in patients with MTHFR deficiency and defects in cbl and limited data were presented for the latter two sub-types of the condition.

Clinical experts have confirmed that betaine is part of the standard treatment plan for homocystinuria in Scotland.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing betaine with standard treatment for patients with homocystinuria. Clinical efficacy data used in the economic evaluation were limited and based mainly on observational studies obtained from the literature. In the base case, it was assumed that if patients did not receive treatment with betaine, 25% would die by age 30 with a utility value of 0.3 and 75% would survive until age 50 with a utility value of 0.5. It was also assumed that with betaine treatment patients would have a utility value of 1 (perfect health) and survive until age 70. Based on these assumptions the manufacturer estimated a cost per QALY of £2,235.

There were a number of problems with the analysis:

- The manufacturer did not include the cost of standard treatments (such as vitamin B6, B12 and dietary advice) in the betaine arm of the model. Experts indicated that betaine treatment would be used in combination with the existing therapies.
- Clinical data used in the economic evaluation appeared to be based on observational studies from the literature; however it was not possible to verify this as the model inputs were not referenced.
- Very little information was provided on the resource use estimates and unit costs used in the model; therefore it was not possible to determine how appropriate these estimates were.
- The utility values were based on assumption. Information from SMC clinical experts indicated that the values used were quite extreme. In particular, experts indicated that it would be unlikely that patients who were treated with betaine would have a utility value of 1 as they would have to follow a strict diet and may still experience some of the symptoms associated with the disease.
- The assumption that 25% of patients not treated with betaine would die by age 30 appears to be based on a study where patients received no form of treatment. In practice, patients would receive standard treatment, suggesting that the mortality rate for those not receiving betaine may be too high.
- A very limited sensitivity analysis was provided on some of the assumptions used in the model. The manufacturer stated a sensitivity analysis would not have been helpful as the number of patients treated with betaine is small. Given that there is a large degree of

uncertainty surrounding treatment with betaine, a more extensive sensitivity analysis would have been extremely helpful.

As a result of the limited clinical data and lack of information provided on the key assumptions used in the economic evaluation, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

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 the submitting company on 21st June 2007. For patients younger than 10 years of age the annual cost of treatment 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). The equivalent cost of the unlicensed betaine monohydrate product that is currently used on a named patient basis is £115 for patients younger than 10 years of age and £230 for patients 10 years of age and older.

Additional information: budget impact

Based on the 12 patients the manufacturer estimated would be treated in Scotland, the annual gross drug cost would be £35k in year 1 rising to £45k in year 5. SMC clinical experts have indicated there may be 20 to 30 patients in Scotland who would be eligible for treatment with betaine.

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 August 2007.

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. Those shaded grey are additional to those supplied with the submission.

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