emerge health

Medicines Classification Committee Secretary
Medsafe
PO Box 5013
Wellington 6145

NEW ZEALAND

25th July 2016

Medicine Classification Application

CYSTADANE (betaine anhydrous) oral powder

Dear Sir/Madam,

Emerge Health, on behalf of the New Zealand Sponsor Healthcare Logistics hereby submits an application to assign the medicinal ingredient *betaine* as an **Intermediate Risk Restricted (pharmacist-only) Medicine** as defined by the New Zealand *Medicines Act 1981*.

This application provides the required information as specified in the Medsafe document "How to change the legal classification of a medicine in New Zealand". The application also refers to the TGA approved Product Information and the Poisons Schedule status in Australia to demonstrate that the benefits afforded by the product substantially outweigh the risk of the product's use.

Emerge Health is seeking classification as an Intermediate Risk Medicine (non-prescription) in preparation for a New Medicine Application (NMA-OTC) to be submitted in New Zealand. This submission follows the collaboration with PHARMAC to have CYSTADANE available in New Zealand for the treatment of the following indications.

INDICATIONS

CYSTADANE is indicated as an adjunct in the treatment of homocystinuria.

CYSTADANE is also indicated to decrease elevated homocysteine blood levels in patients of all age groups with:

1. *cystathionine beta-synthase (CBS deficiency) type of homocystinuria, or*
2. *5, 10- methylenetetrahydrofolate reductase deficiency (MTHFR deficiency), or*
3. *cobalamin cofactor metabolism defect (cbl defect) type of homocystinuria.*

CYSTADANE is also indicated to increase methionine and S-adenosylmethionine blood levels in patients with 5, 10- methylenetetrahydrofolate reductase deficiency (MTHFR deficiency) and cobalamin cofactor metabolism defect (cbl defect) type of homocystinuria.

Methionine blood levels may become greatly elevated in CBS deficiency type patients. However, monitoring of patients with high methionine blood levels for many years has not revealed any toxicities or other clinical problems.

Cystadane can be administered along with folate, vitamin B_6, and vitamin B_{12} (cobalamin).

We trust that the information provided demonstrates the best benefit/risk ratio of betaine to New Zealand citizens when classified as an Intermediate Risk medicine. Please, however do let us know if you would like further information or clarification.

We look forward to the outcome of the Committee's review.

Yours sincerely,

Edward (Ned) Kilpatrick
Regulatory Affairs Manger
Emerge Health Pty Ltd
n.kilpatrick@emergehealth.com.au

Part A

International non-proprietary name (INN):

1-carboxy-N, N, N-trimethyl-hydroxide, Inner salt

- Chemical name:

N-trimethylglycine, methanaminium

- Other names:

Betaine anhydrous
Methanaminium, 1-carboxy-N, N, N-trimethyl-hydroxide, inner salt;
(Carboxymethyl) trimethyl ammoniumhydroxide, inner salt

- Chemical Abstracts Service (CAS) number: 107 - 43 - 7
- European Commission (EINECS) number: 203 - 490 - 6

Proprietary name:

- CYSTADANE

Applicant:

- Emerge Health
  Suite 3, Level 1, 2 Theatre Place
  Canterbury VIC 3126
  Australia

  On behalf of:

  Healthcare Logistics
  58 Richard Pearse Drive, Airport Oaks
  Mangere 2022
  Auckland

  PO Box 62 027
  Sylvia Park 1644

  NB: All correspondence relating to this application should be forwarded to Ned Kilpatrick, Regulatory Affairs Manager, Emerge Health, n.kilpatrick@emergehealth.com.au

Dose form and Strength:

CYSTADANE is supplied as betaine anhydrous in oral powder form. Betaine anhydrous is the sole ingredient in the drug product. The product is provided with a scoop. One level scoop (1.7 mL) is equivalent to 1.0 gram of betaine anhydrous powder. Betaine is tested to ensure an assay value of 99.0 – 101.0% (on a dry basis).

Pack size and Qualifications:

CYSTADANE is supplied as one presentation, a 180g resealable bottle. The container closure system consists of a 300 mL round, opaque, white, HDPE bottle with a white, polypropylene child resistant closure. The closure is lined with a foil seal that is heat sealed to the lip of the bottle. A 1.7 mL white polystyrene measuring spoon is enclosed in the carton for each bottle. Each bottle contains sufficient betaine for 30 days treatment using 6 grams/day.

Indication:

The proposed Indication for the forthcoming NMA is:

CYSTADANE is indicated as an adjunct in the treatment of homocystinuria.

CYSTADNE is also indicated to decrease elevated homocysteine blood levels in patients of all age groups with:

1. *cystathionine beta-synthase (CBS deficiency) type of homocystinuria, or*
2. *5, 10- methylenetetrahydrofolate reductase deficiency (MTHFR deficiency), or*
3. *cobalamin cofactor metabolism defect (cbl defect) type of homocystinuria.*

CYSTADANE is also indicated to increase methionine and S-adenosylmethionine blood levels in patients with 5, 10- methylenetetrahydrofolate reductase deficiency (MTHFR deficiency) and cobalamin cofactor metabolism defect (cbl defect) type of homocystinuria.

Methionine blood levels may become greatly elevated in CBS deficiency type patients. However, monitoring of patients with high methionine blood levels for many years has not revealed any toxicities or other clinical problems.

Cystadane can be administered along with folate, vitamin B_6, and vitamin B_{12} (cobalamin).

Present Classification:

New application – betaine is not yet classified in New Zealand.

Classification sought:

Intermediate Risk Restricted (pharmacist only) Medicine

Classification in other countries:

Australia – Betaine is an ARTG Registered, Non-Prescription Medicine, not scheduled (not considered by the Advisory Committee for the Scheduling of Medicines). Refer to attached "ARTG current entry Summary".

European Union – Prescription Medicine as adjunct therapy for homocystinuria. Refer to attached EU-SPC.

United States – Prescription Medicine in the treatment of homocystinuria. Refer to attached US-PI.

Canada – Prescription Medicine in the treatment of homocystinuria. Refer to attached Health Canada Product Monograph.

Extent of use in New Zealand and Elsewhere during 2015:

New Zealand: 82 units

Australia: 1,133 units

Dates of original consent to distribute:

New Zealand: CYSTADANE supplied as Section 29 Medicine since October 2012.

Australia: TGA registered (unscheduled) medicine since October 1996.

Labelling:

Refer to Attachment 1 for a copy of the Australian TGA approved Product Information for CYSTADANE. The Australian Product Information document is proposed for use as the Data Sheet for New Zealand.

Warning Statements:

The following is an excerpt from the Precautions section of the Australian Product Information:

Hypermethioninemia

Patients with homocystinuria due to cystathionine beta-synthase (CBS) deficiency may also have elevated plasma methionine concentrations. Treatment with Cystadane may further increase methionine concentrations due to the remethylation of homocystine to methionine. Cerebral oedema has been reported in patients with hypermethioninemia including a few patients treated with Cystadane. Plasma methionine concentrations should be monitored in patients with CBS deficiency. Plasma methionine concentrations should be kept below 1,000 µmol/L through dietary modification and, if necessary, a reduction of Cystadane dose.

Information for Patients

1. *Measure with the scoop provided.*
2. *One level scoop (1.7 mL) is equivalent to 1.0 grams of betaine anhydrous powder. Measure the number of scoops your physician has prescribed.*
3. *Mix with 120 – 180 mL of water and drink immediately.*

Always replace the cap tightly after using.

Laboratory Tests

Homocysteine plasma levels can be determined by utilisation of various commercially available amino acid analysers.

Use in pregnancy (Category C)

Animal reproduction studies have not been conducted with betaine. It is also not known whether betaine can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Cystadane should be given to a pregnant woman only if clearly needed.

Use in lactation

It is not known if betaine is excreted in human milk (although it's metabolic precursor, choline, occurs in high levels in human milk). Because many drugs are excreted in human milk, caution should be exercised when Cystadane is administered to a nursing mother.

Paediatric Use

The majority of cases of homocystinuria patients treated with betaine have been paediatric patients. The disorder, in its most severe form, can be manifested within the first months or years of life by lethargy, failure to thrive, development delays, seizures or eye lens displacement. Patients have been treated successfully without adverse effects within the first months or years of life with dosages of 6 grams per day or more of betaine, with resultant biochemical and clinical improvement. However, dosage titration may be preferable in paediatric patients (see ***DOSAGE AND ADMINISTRATION****).*

Carcinogenicity, mutagenicity and impairment of fertility

Long term carcinogenicity and fertility studies have not yet been conducted on betaine. No evidence of mutagenic potential was demonstrated in the following tests:

Metaphase Analysis of Human Lymphocytes; Bacterial Reverse Mutation Assay, and Mouse Micronucleus Test.

Other products affected by this change:

Not applicable. There are no other products containing the same active ingredient that are registered in New Zealand.

Part B

Benefits to consumer and public expected

Betaine anhydrous, supplied under the tradename CYSTADANE, is intended to be used for the adjunctive treatment of homocystinuria due to cystathionine β-synthase (CBS) deficiency, 5, 10-methylenetetrahydrofolate (MTHFR) reductase deficiency or cobalamin cofactor (cbl) metabolism deficiency. Poorly controlled homocystinuria is associated with very serious clinical outcomes which include mental retardation, cardiac arterial disease, ectopia lentis and osteoporosis. Poor control may also increase mortality in patients.

Appropriate chronic treatment to lower hyperhomocysteinaemia is effective in reducing the potentially life-threatening vascular risk in patients with homocystinuria (Yap 2003). Emerge Health has been advised by Australian metabolic specialists that CYSTADANE is an important component of treatment for patients with homocystinuria.

Potential risk of harm to the consumer

Refer to **Adverse Effects** and **Potential for misuse or abuse** below.

Ease of self diagnosis or diagnosis by a pharmacist

Diagnosis of homocystinuria is performed by specialised metabolic physicians, who together with dieticians develop an appropriate management plan for patients. The control of homocystinuria is facilitated through the adjunctive therapy with folate, vitamin B_6 (pyridoxine) and vitamin B_{12} (cobalamin). These adjunctive agents are supplied through pharmacy or general sale (as noted below).

As per the proposed Data Sheet, periodic assessment of plasma methionine concentrations is recommended. This periodic assessment involves the review of the patient's health status by specialist metabolic physicians. Supply of betaine as a pharmacist-only medicine would therefore allow the pharmacist to check with the patient at point of supply on when their plasma levels were last evaluated. This will also allow the pharmacist to review the patient's ongoing regimen and consolidate the supply of the other adjunctive therapies at the same time. These other adjunctive therapies are included in the New Zealand classification database as follows:

Folic acid:	General Sale (for oral use in medicines containing 500 micrograms or less per recommended daily dose; in parenteral nutrition replacement preparations)

	Pharmacy Medicine (for oral use in medicines containing more than 500 micrograms per recommended daily dose)
Vitamin B_6	General sale (in medicines containing 200 mg or less as per recommended daily dose)
	Prescription Medicine (in medicines containing more than 200 mg as per recommended daily dose)
Vitamin B_{12}	Not classified

Relevant comparative data for like compounds

The standard therapy for the treatment of homocystinuria is an existing treatment regimen involving vitamin B_6, vitamin B_{12} and folic acid, in addition to a methionine restricted diet with cystine supplements.

A study conducted in Australia (Wilcken et al 1985), reported on the effectiveness of adding betaine (6 – 9g/day) to an existing regimen of folic acid (5mg/day) and vitamin B_6 (100 – 200 mg/day). The addition of betaine to the treatment regimen demonstrated further reductions in plasma total homocysteine levels.

Interactions with other medicines

No interactions with other medicines are specified in the Australian Product Information.

Contraindications and precautions

There are no Contraindications for CYSTADANE specified in the Australian Product Information.

For Precautions, refer to **Warning Statements** above.

Possible resistance

None known.

Adverse effects

As listed in the Australian Product Information:

ADVERSE EFFECTS

Adverse reactions to betaine have been minimal. Possible adverse effects inclusion nausea, gastrointestinal distress and diarrhoea.

A few cases of cerebral oedema have been reported secondary to severe hypermethioninemia in patients with cystathionine beta-synthase (CBS) deficiency treated with Cystadane. See ***PRECAUTIONS: Hypermethioninemia****.*

Potential for misuse or abuse

No information is available on misuse or abuse. As listed in the Australian Product Information:

OVERDOSAGE

No incidence of overdosage has been reported.