NEW ZEALAND DATA SHEET

1 PRODUCT NAME (STRENGTH PHARMACEUTICAL FORM)

CYSTADANE 1 g powder for oral administration

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of powder contains 1 g of betaine anhydrous.

3 PHARMACEUTICAL FORM

Oral powder.
White crystalline free flowing powder.

CYSTADANE (betaine anhydrous powder) for oral administration is an antihomocysteine agent. CYSTADANE is a white, granular powder. It contains no ingredient other than anhydrous betaine. Betaine anhydrous powder is soluble in water, methanol and ethanol. It is sparingly soluble in ether.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

Patients response to CYSTADANE can be monitored by homocysteine plasma levels (see Section 4.2 **DOSE AND METHOD OF ADMINISTRATION).** Response usually occurs within a week and steady state within a month.

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).

4.2 Dose and method of administration

The usual dose used in adults and paediatric patients is 6 grams per day administered orally in divided doses of 3 grams two times per day. Dosages of up to 20 grams per day have been necessary to control homocysteine levels in some patients. In paediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day and then increased weekly by 100 mg/kg increments. Dosage in all patients can be gradually increased until plasma homocysteine is undetectable or present only in small amounts.

The prescribed amount of CYSTADANE powder should be measured using the measuring scoops provided and then dissolved in 120 – 180 mL of water for immediate ingestion. Three measuring spoons are provided which dispense either 100 mg, 150 mg or 1 g of betaine anhydrous. It is recommended that a heaped measuring spoon is removed from the container and a flat surface e.g. base of a knife is drawn across the top of the measure. This will give the following doses: small measure 100 mg, middle size measure 150 mg and large measure 1 g of betaine anhydrous.

4.3 Contraindications

Hypersensitivity to the active substance.

4.4 Special warnings and precautions for use

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 scoops provided.
2. 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.

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 Section 4.2 **DOSE AND METHOD OF 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.

4.5 Interaction with other medicines and other forms of interaction

None known.

4.6 Fertility, pregnancy and lactation

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.

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.

4.7 Effects on ability to drive and use machines

CYSTADANE has no influence on the ability to drive and use machines.

4.8 Undesirable effects

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

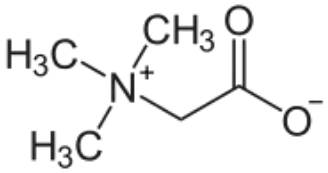
A few cases of cerebral oedema have been reported secondary to severe hypermethioninemia in patients with cystathionine beta-synthase (CBS) deficiency treated with CYSTADANE (see Section 4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE; Hypermethioninemia).**

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, ATC code: A16AA06

5.1 Pharmacodynamic properties

The chemical name of betaine anhydrous powder is trimethylglycine. Its structural formula is:



When administered in recommended oral dosage to children or adults, CYSTADANE acts as a methyl group donor in the remethylation of homocysteine to methionine in patients with homocystinuria. As a result, toxic blood levels of homocysteine are reduced in these patients, usually to 20 – 30 percent or less of pre-treatment levels.

Elevated homocysteine blood levels are considered to cause serious clinical problems in patients such as cardiovascular thrombosis, leading to premature death, osteoporosis, skeletal abnormalities, and optic lens dislocation. Studies have demonstrated that homocysteine plasma levels decrease in 98% of patients taking betaine. Clinical improvement was observed in 77% of patients, and in an additional 21% of patients, disease progression was prevented. Many of these patients had not responded to previous therapies including vitamin B_6, vitamin B_{12} (cobalamin), and folate.

Studies have demonstrated betaine to be effective in the three types of homocystinuria, i.e. cystathionine beta-synthase deficiency (CBS deficiency); 5, 10-methylenetetrahydrofolate reductase deficiency (MTHFR deficiency); and cobalamin cofactor metabolism defect (cbl defect).

Betaine has also been demonstrated to increase plasma methionine and S-adenosylmethionine (SAM) in MTHFR deficiency and cbl defect patients who have low levels of methionine and SAM, which are thought to be the cause of demyelination and other neurologic problems.

In CBS deficient patients, increases in methionine levels have been marked. However, these have not been of clinical consequence as evidenced by treatment of CBS deficient patients with betaine for up to 11 years with no adverse effect.

Betaine occurs naturally in the body. It is a metabolite of choline and present in small amounts in foods such as beets, spinach, cereals and seafood.

5.2 Pharmacokinetic properties

Pharmacokinetic studies of betaine are not available. However, pharmacodynamic measurements, i.e. monitoring of plasma homocysteine levels, have demonstrated the onset of action of betaine is within several days and that steady state in response to dosage is achieved within several weeks. Patients have taken betaine for many years without evidence of tolerance.

5.3 Preclinical safety data

No incidence of overdosage has been reported.

Long term toxicology studies of betaine in animals have not been conducted. In an acute toxicology study in rats, the LD_{50} was 11,179 mg/kg.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years from date of manufacture stored below 25°C.
3 months opened stored below 25°C.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

HDPE bottles with a child resistant closure.
Each pack contains 1 bottle with 180 g of powder.
Three measuring spoons are included in each pack.
Three measuring spoons (pink, blue, green) dispense, respectively, 1 g, 150 mg and 100 mg of betaine anhydrous powder.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
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9 DATE OF FIRST APPROVAL

24 May 2018

10 DATE OF REVISION OF THE TEXT

June 2019

Summary table of changes:

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1, 6.5	Minor editorial changes