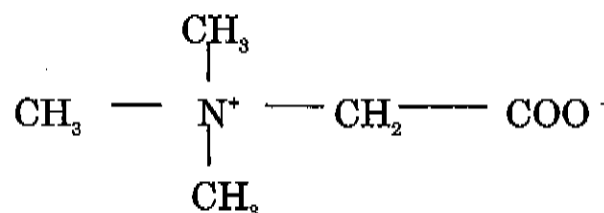


Cystadane™
(betaine anhydrous powder)

DESCRIPTION

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

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

**CLINICAL PHARMACOLOGY**

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 decreased 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 B₆, vitamin B₁₂ (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.

Pharmacokinetic studies of betaine are not available. However, pharmacodynamic measurements, i.e., monitoring of plasma homocysteine levels, have demonstrated that 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.

INDICATIONS AND USAGE

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)

types 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) types of homocystinuria.

Patient response to Cystadane can be monitored by homocysteine plasma levels (see DOSAGE AND 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 B₆, and vitamin B₁₂ (cobalamin).

CONTRAINDICATIONS

None known.

PRECAUTIONS

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 $\mu\text{mol/L}$ 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 analyzers.

Drug Interactions: None known.

Carcinogenesis, mutagenesis, impairment of fertility: Long term carcinogenicity and fertility studies have not 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.

Pregnancy: 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 reproduction capacity. Cystadane should be given to a pregnant woman only if clearly needed.

Nursing mothers: It is not known whether betaine is excreted in human milk (although its metabolic precursor, choline, occurs at high levels in human milk). Because many drugs are excreted in human milk, caution should be exercised when Cystadane is administered to a nursing woman.

Paediatric use: The majority of case studies of homocystinuria patients treated with betaine have been of 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, developmental 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).

ADVERSE REACTIONS

Adverse reactions to betaine have been minimal. Possible adverse effects include 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.

DOSAGE AND ADMINISTRATION

The usual dosage used in adult 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 with the measuring scoop provided (one 1.7 mL scoop is equal to 1 gram of betaine anhydrous powder) and then dissolved in 120 - 180 mL of water for immediate ingestion.

OVERDOSAGE

No incidents of overdosage have been reported.

Animal Toxicology: Long term toxicology studies of betaine in animals have not been conducted. In an acute toxicology study in rats, the LD₅₀ was 11,179 mg/kg.

HOW SUPPLIED

Cystadane is available in bottles of 180 grams. One scoop (1.7 mL) is equal to 1 gram of betaine anhydrous powder.

Store below 25°C.

DISTRIBUTED BY

Orphan Australia Pty. Ltd.
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This Product Information was approved by the Therapeutic Goods Administration on 27 September 1996.

Date of most recent amendment: 22 June 2005.