PRODUCT MONOGRAPH

CYSTADANE®

(betaine anhydrous powder for oral solution)

THERAPEUTIC CLASSIFICATION

Anti-Homocysteine Agent

ACTION AND CLINICAL PHARMACOLOGY

Clinical Pharmacology:

CYSTADANE® (betaine anhydrous powder for oral solution) is an agent for the treatment of homocystinuria. 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 associated with clinical problems such as cardiovascular thrombosis, osteoporosis, skeletal abnormalities, and optic lens dislocation. Plasma levels of homocysteine were decreased in nearly all patients treated with betaine. In observational studies without concurrent controls, clinical improvement was reported by treating physicians in about three-fourths of patients taking betaine. Many of these patients were also taking other therapies such as vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin), and folate with variable biochemical responses. In most cases studied, adding betaine resulted in a further reduction in homocysteine.

Betaine was observed to lower plasma homocysteine levels in the three types of homocystinuria, i.e., cystathionine beta-synthase (CBS) deficiency; 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency; and cobalamin cofactor metabolism (*cbl*) defect.

Betaine has also been demonstrated to increase low plasma methionine and S-adenosylmethionine (SAM) levels in patients with MTHFR deficiency and *cbl* defect.

In CBS-deficient patients, large increases in methionine levels have been observed. However, the increased methionine levels do not appear to have been associated with adverse clinical consequences.

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

INDICATIONS AND CLINICAL USE

CYSTADANE (betaine anhydrous powder for oral solution) is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood levels. Included within the category of homocystinuria are deficiencies or defects in:

1. cystathionine beta-synthase (CBS),
2. 5,10-methylenetetrahydrofolate reductase (MTHFR),
3. cobalamin cofactor metabolism (*cbl*).

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.

CYSTADANE has been administered concomitantly with vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin), and folate.

CONTRAINDICATIONS

There are no known contraindications for CYSTADANE (betaine anhydrous powder for oral solution).

WARNINGS

There are no warnings for CYSTADANE (betaine anhydrous powder for oral solution).

PRECAUTIONS

General: Therapy with CYSTADANE (betaine anhydrous powder for oral solution) should be directed by physicians knowledgeable in the management of patients with homocystinuria.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity and fertility studies have not been conducted on betaine. No evidence of genotoxicity was demonstrated in the following tests: Metaphase Analysis of Human Lymphocytes; Bacterial Reverse Mutation Assay; and Mouse Micronucleus Test.

Pregnancy: Animal reproduction studies have not been conducted with betaine. It is also not known whether betaine can cause fetal harm when administered to a pregnant woman or can affect reproductive 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.

Pediatric Use: The majority of case studies of homocystinuria patients treated with betaine have been pediatric 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 optic 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 pediatric patients (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse reactions to betaine have been minimal. In a survey study of physicians who had treated a total of 111 homocystinuria patients with betaine, the types of adverse effects and the number of patients experiencing them were as follows:

Nausea	2
GI distress	2
Diarrhea	1
Caused odour	1

Questionable psychological changes	1
Aspirated the powder	1
Unspecified problem	1

No other types of adverse effects have been reported.

OVERDOSAGE

In an acute toxicology study in rats, death frequently occurred at doses equal to or greater than 10,000 mg/kg. When doses are expressed and compared on the basis of body surface area, the LD_{50} is equivalent to 5-18 times the intended human clinical dose.

DOSAGE AND ADMINISTRATION

The usual dosage in adult and pediatric 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 pediatric 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 (betaine anhydrous powder for oral solution) should be measured with the measuring scoop provided (one level 1.7 cc scoop is equal to 1 gram of betaine anhydrous powder) and then dissolved in 4 to 6 ounces of water, juice, milk, or formula, or mixed with food for immediate ingestion.

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Name: trimethylglycine

Structural Formula:

Molecular Formula: $C_5H_{11}NO_2$

Molecular Weight: 117.15

Description: CYSTADANE is a white granular, hygroscopic powder. Betaine anhydrous powder is very soluble in water, soluble in methanol and ethanol, and sparingly soluble in ether.

Composition

Active Ingredient: betaine anhydrous

Non-medicinal Ingredients: There are no non-medicinal ingredients

Stability and Storage Recommendations

Store at room temperature, 15^0 - 30^0C (59^0 - 86^0F). Protect from moisture.

Reconstituted Solutions

One level scoop (1.7 cc) is equivalent to 1 gram of betaine anhydrous powder. Measure the number of scoops your physician has prescribed. Mix with 4 to 6 ounces of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest immediately.

AVAILABILITY OF DOSAGE FORMS

CYSTADANE (betaine anhydrous powder for oral solution) is available in plastic bottles containing 180 grams of betaine. Each bottle is equipped with a child-resistant cap and is supplied with a polystyrene measuring scoop. One level (1.7 cc) is equal to 1 gram of betaine anhydrous powder.

CYSTADANE is available through a specialty distribution system. Please call 1-800-900-4267 or your wholesaler for ordering information.

INFORMATION FOR THE CONSUMER

1. Shake bottle lightly before removing cap.
2. Measure with the scoop provided.
3. One level scoop (1.7 cc) is equivalent to 1 gram of betaine anhydrous powder. Measure the number of scoops your physician has prescribed.
4. Mix with 4 to 6 ounces of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest immediately.

Always replace the cap tightly after using. Protect from moisture.

PHARMACOLOGY

Betaine decreases plasma homocysteine levels by serving as a methyl donor for the remethylation of homocysteine to methionine in an important alternative pathway. The reaction is catalyzed by betaine-homocysteine methyltransferase which does not require the cofactors 5-methyltetrahydrofolate or methylcobalamin for the conversion of homocysteine to methionine.

Since it is not dependent on the cofactors, betaine is effective in the treatment of all three primary types of homocystinuria. Betaine has also been demonstrated to increase low plasma methionine and S-adenosylmethionine (SAM) levels in the 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency and cobalamin cofactor metabolism (*cbl*) defect types of homocystinuria.

Betaine is available in small quantities in foods such as beets, spinach, cereals, and seafood. It is also available as a metabolite of choline, another dietary component. However, the amount of betaine available from these sources is insufficient to control the greatly elevated plasma levels present in patients with homocystinuria.

When pharmacologic doses of betaine are given to patients with homocystinuria, elevated levels of homocysteine are decreased. Plasma levels of homocysteine were decreased in nearly all patients treated with betaine. In observational studies without concurrent controls, clinical improvement was reported by treating physicians in about three-fourths of patients taking betaine. Many of these patients were also taking other therapies such as B_6 (pyridoxine), vitamin B_{12} (cobalamin), and folate with variable biochemical responses. In most cases studied, adding betaine resulted in a further reduction of homocysteine levels.

TOXICOLOGY

The acute oral toxicity of betaine anhydrous was investigated in five groups of five male and five female CD rats. The animals were starved overnight prior to dosing. The test material was administered on Day 1 at dosages in the range of 5,000 - 20,000 mg/kg, at a volume-dosage of 40 mL/kg in distilled water.

The acute oral median lethal dosage (LD50), 95% confidence limits and slope of the dose response curve were:

	LD50 (mg/kg)	**95% CI**	**Slope (degrees)**

Male	11,204	8,616-13,792	88
Female	11,148	9,929-12,367	83
Combined	11,179	10,454-11,904	85

Signs of toxicity included lethargy, decreased motor activity, prone posture, ataxia, muscle tremor, breathing irregularities, piloerection, ungroomed appearance, salivation, hunched posture and diarrhea.

A dose range finding study was carried out on betaine monohydrate using concentrations up to 10,000 mcg/mL. Based on the results obtained, concentrations of 1,000, 3,333 and 10,000 mcg/mL in the absence and presence of S-9 were selected for a cytogenetic study of metaphase analysis of human lymphocytes. Betaine monohydrate caused no statistically significant increases in chromosome aberrations, nor did the aberrations scored from a dose response relationship in either the absence or presence of S-9. It was concluded that betaine monohydrate was not a clastogen to human lymphocytes under the conditions of this study.

Betaine monohydrate was tested *in vitro* by the Ames plate incorporation method for its ability to induce mutations in five histidine dependent auxotrophic mutants of *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100. Two independent mutation tests were performed, each in both the presence and absence of a metabolic activation system (S-9) at the following dosages: 5,000, 1,000, 200, 40 and 8 mcg/plate. Betaine monohydrate produced no significant increases in the number of revertants, with any of the tester strains, in either of the two experiments performed. It was concluded that betaine monohydrate was not mutagenic in the above test.

A mouse micronucleus test was conducted at dosages of 0.5, 1, 1.5 and 2 g/kg using betaine monohydrate. Toxicity of betaine monohydrate to the bone marrow, measured by reduced PCE/NCE (polychromatic erythrocytes/normochromatic erythrocytes) ratios, was not observed. Compared to the appropriate control groups, no significant increases in micronucleated PCE were seen for any group of animals dosed with betaine monohydrate. The numbers of micronuclei scored in treated animals showed normal variation about the control animals. It was concluded that betaine monohydrate does not induce micronuclei in the bone marrow of mice dosed at levels up to a dose of 2 g/kg by the oral route.

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