PRODUCT MONOGRAPH

[Pr]Cystadane®

betaine anhydrous powder for oral solution

1 gram/1.7 cc scoop

Professed Standard

Anti-Homocysteine Agent

Recordati Rare Diseases Canada Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	1 g per 1.7 cc scoop	none *For a complete listing see Dosage Forms, Composition and Packaging section*

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 and methionine plasma levels (See DOSAGE AND ADMINISTRATION). Response usually occurs within a week and maximum response within four to six weeks.

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

Geriatrics:

Clinical data differentiating younger adults and adults >65 years are not available.

Pediatrics:
Homocystinuria 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 with CYSTADANE. Dosage titration is preferable in the pediatric population. See WARNINGS AND PRECAUTIONS, Pediatric Use, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

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

WARNINGS AND 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 and Mutagenesis
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.

Endocrine and Metabolism
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 homocysteine to methionine. Cerebral edema 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.

Special Populations

Pregnant Women: 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 Women: 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.

Pediatrics: 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 with betaine within the first months or years of life, without adverse effects. Dosage titration is recommended in pediatric patients (See DOSAGE AND ADMINISTRATION).

Geriatrics (> 65 years of age): Clinical data is not available.

Monitoring and Laboratory Tests

Plasma homocysteine levels should be monitored in patients treated with CYSTADANE. In patients with CBS deficiency, plasma methionine concentrations should be monitored and kept below 1,000 μmol/L. See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism - Hypermethioninemia.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Post-Market Adverse Drug Reactions

A few cases of cerebral edema have been reported secondary to severe hypermethioninemia in patients with cystathionine beta-synthase (CBS) deficiency treated with CYSTADANE. See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism - Hypermethioninemia.

DRUG INTERACTIONS

Overview

There are no known interactions with CYSTADANE. CYSTADANE has been administered concomitantly with vitamin B_6 (pyridoxine), B_{12} (cobalamin), and folate.

Because of the potential for CYSTADANE to further increase plasma methionine concentrations in patients with cystathionine beta-synthase (CBS) deficiency, plasma methionine concentrations should be monitored in these patients and kept below 1,000 µmol/L, through dietary modification and, if necessary, a reduction of CYSTADANE dose.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dose titration is recommended in the pediatric population. See below.

In patients with CBS deficiency, plasma methionine concentrations should be monitored and kept below 1,000 µmol/L, through dietary modification, and if necessary, a reduction in CYSTADANE dose.

Recommended Dose and Dosage Adjustment

The usual dosage in adult 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, dosage may be started at 100 mg/kg/day and then increased once by a 50 mg/kg increment after four to six weeks. In one study, pharmacokinetic and pharmacodynamic simulation indicated minimal benefit from exceeding a twice-daily dosing schedule and a 150 mg/kg/day dosage for betaine. The maximum amount of dosage in children must not exceed 6 grams per day.

Plasma total homocysteine and methionine concentrations should be monitored in patients with CBS deficiency. See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism - Hypermethioninemia.

Missed Dose

A missed dose should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the patient resume their regular dosing schedule.

Administration

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 (120 to 180 mL) of water, juice, milk, or formula, or mixed with food for immediate ingestion.

OVERDOSAGE

Treatment with CYSTADANE may further increase methionine concentrations due to the remethylation of homocysteine to methionine. Cerebral edema 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. In the pediatric population, there appears to be

only a marginal benefit from exceeding 150 mg/kg/day.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacodynamics

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, usually to 20-30 percent or less of pre-treatment levels. The maximum reduction in plasma levels of homocysteine was achieved in several weeks.

Betaine was observed to lower plasma homocysteine levels in the three types of homocystinuria, i.e., cystationine 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 Sadenosylmethionine (SAM) levels in patients with MTHFR deficiency and *cbl* defect.

In CBS-deficient patients, large increases in methionine over baseline levels have been observed.

Pharmacokinetics

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

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 maximum response to dosage is achieved within several weeks. Patients have taken betaine for many years without evidence of tolerance.

STORAGE AND STABILITY

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

Replace the cap tightly after using.

SPECIAL HANDLING INSTRUCTIONS

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 (120 to 180 mL) of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest immediately.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Active Ingredient: betaine anhydrous

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

CYSTADANE (betaine anhydrous powder for oral solution) is available in plastic bottles containing of 180 grams of betaine anhydrous. Each bottle is equipped with a child-resistant cap and is supplied with a polypropylene 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 905-827-1300 or your wholesaler for ordering information.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

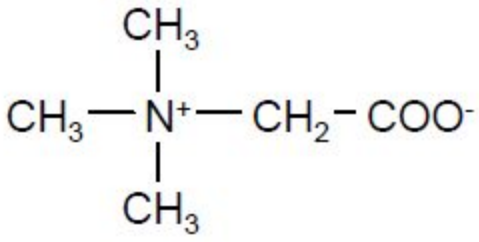
Drug Substance

Proper name: betaine anhydrous

Chemical name: trimethylglycine

Molecular formula and molecular mass: $C_5H_{11}NO_2$ 117.15

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

Clinical trial data is not available.

DETAILED 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 5methyltetrahydrofolate 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.

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 rangefinder was carried out on betaine monohydrate using concentrations up to 10,000 µg/mL. Based on the results obtained, concentrations of 1,000, 3,333 and 10,000 µg/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 mutations 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 µg/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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PART III: CONSUMER INFORMATION

[Pr]Cystadane®

Betaine anhydrous powder for oral solution

This leaflet is part III of a three-part "Product Monograph" designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CYSTADANE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CYSTADANE is used in the treatment of homocystinuria. Homocystinuria is a rare disease in which abnormal levels of a naturally occurring amino acid, homocysteine, is found in blood and urine. Homocystinuria is caused by a lack of enzymes, cystathionine beta-synthase (CBS) or methlenetetrahydrofolate reductase (MTHFR), or a defect in the cobalamin cofactor metabolism (cbl).

What it does:
CYSTADANE reduces the extra homocysteine from the body by aiding in the conversion of homocysteine to methionine.

When it should not be used:
Do not use if you (or your child) are allergic to betaine (bay-ta-een).

What the medicinal ingredient is:
CYSTADANE contains the medicinal ingredient betaine (bay-ta-een).

What the important nonmedicinal ingredients are:
There are no nonmedicinal ingredients in CYSTADANE.

What dosage forms it comes in:
CYSTADANE is available in a powder form for oral solution.

CYSTADANE is available in plastic bottles of 180 g. Each bottle contains a measuring scoop. One level scoop (1.7 cc) equals 1 gram of betaine anhydrous powder.

WARNINGS AND PRECAUTIONS

BEFORE you use CYSTADANE talk to your doctor or pharmacist:

- About your past and present health problems and medical condition.
- If you are pregnant, plan to become pregnant, or are breast-feeding.

CYSTADANE may cause hypermethioninemia resulting in cerebral edema. Methionine blood levels should be monitored while taking CYSTADANE.

INTERACTIONS WITH THIS MEDICATION

Before you (your child) use CYSTADANE tell your (your child's) doctor or pharmacist if you (your child) take or plan to take any other medication including prescription and non- prescription medication, vitamin supplements, and natural health products. CYSTADANE has been used with vitamin B_6 (pyridoxine), B_{12} (cobalamin), and folate.

PROPER USE OF THIS MEDICATION

The prescribed dose of CYSTADANE should be measured with the measuring scoop provided. One level 1.7 cc scoop is equal to 1 gram of betaine anhydrous powder. Mix the measured dose with 120 to 180 mL (4 to 6 ounces) of water, juice, milk, or infant formula until completely dissolved, or mix with food. Take immediately after preparing dose.

Adult dose:
Take as prescribed by your doctor. The usual dose is 6 grams per day taken orally in divided doses of 3 grams two times per day. Your doctor may adjust your dose as needed.

Children dose:
In children, the dose is based on body weight. Your doctor may prescribe an initial dose of 100 mg/kg body weight per day and then may increase the dose by 50 mg/kg body weight after 4 to 6 weeks to a maximum of 150 mg/kg/day. The maximum dose must not exceed 6 grams per day.

Overdose:
If you think you or someone else has taken an overdose of CYSTADANE, tell your doctor or go to the emergency room at the nearest hospital.

Missed Dose:
Take the missed dose of CYSTADANE as soon as you remember. If it is almost time for your next dose, skip the one you missed and go back to your regular dosing schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include: nausea, diarrhea, body odour, stomach and intestinal problems. Consult your doctor or pharmacist if any side effects continue or are bothersome.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Cerebral edema (abnormal pooling of fluid in the brain with associated symptoms of severe headache, nausea, vomiting, loss of eyesight, confusion and coma)			√
Allergic reaction (rash, swelling of the lips, face or neck, difficulty breathing or speaking)			√

This is not a complete list of side effects. For any unexpected effects while taking CYSTADANE, contact your doctor or pharmacist.

HOW TO STORE IT

Store CYSTADANE at room temperature (15°-30°C). Replace cap tightly after using. Protect from moisture.

Keep all medicines away from children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the Canadian distributor, Recordati Rare Diseases Canada Inc., at: 905-827-1300

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