HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Cystadane safely and effectively. See full prescribing information for Cystadane.

Cystadane® (betaine anhydrous for oral solution) powder

Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------

Cystadane is a methylating agent indicated for the treatment of homocystinuria to decrease elevated homocysteine blood levels. Included within the category of homocystinuria are (1):

- Cystathionine beta-synthase (CBS) deficiency
- 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
- Cobalamin cofactor metabolism (cbl) defect

----------DOSAGE AND ADMINISTRATION----------

- Usual dose in adult and pediatric patients is 6 grams per day, administered orally in divided doses of 3 grams two times a day. (2)
- In children less than 3 years of age, may initiate dosing at 100 mg/kg/day, divided in twice daily doses, and then increased weekly by 50 mg/kg increments. (2)
- Dose can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts .(2)
- Monitor patient response by plasma homocysteine levels. (2)
- Prescribed amount of Cystadane should be measured with the measuring scoop provided and then dissolved in 4 to 6 ounces of water, juice, milk, or formula, or mixed with food for immediate ingestion. (2)

----------DOSAGE FORMS AND STRENGTHS----------

- Powder for oral solution available in bottles containing 180 grams of betaine anhydrous. (3)

----------CONTRAINDICATIONS----------

- None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypermethioninemia: Cystadane may worsen elevated plasma methionine concentrations in patients with CBS deficiency. Cerebral edema has been reported in patients receiving Cystadane. (5.1)
- Monitoring: Monitor plasma methionine concentrations in patients with CBS deficiency. Keep plasma methionine concentrations below 1,000 µmol/L through dietary modification and, if necessary, a reduction of Cystadane dose. (5.1)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (incidence > 2%) were nausea and gastrointestinal distress, based on physician survey.

To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Animal reproduction studies have not been conducted with Cystadane. Use only if clearly needed. (8.1)
- Nursing women: It is not known whether Cystadane is excreted in human milk. Use only if clearly needed. (8.3)
- Pediatrics: Pediatric patients ranging in age from 24 days to 17 years have been treated with Cystadane. Children younger than 3 years of age may benefit from dose titration.

See 17 for PATIENT COUNSELING INFORMATION.

Revised 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Cystadane® (betaine anhydrous for oral solution) is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood levels. Included within the category of homocystinuria are:

- Cystathionine beta-synthase (CBS) deficiency
- 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
- Cobalamin cofactor metabolism (cbl) defect

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The usual dosage in adult and pediatric patients is 6 grams per day administered orally in divided doses of 3 grams twice daily. In pediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day divided in twice daily doses, and then increased weekly by 50 mg/kg increments. Therapy with Cystadane should be directed by physicians knowledgeable in the management of patients with homocystinuria. Patient response to Cystadane can be monitored by homocysteine plasma levels. Dosage in all patients can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts. Response (by homocysteine plasma levels) usually occurs within several days and steady state within a month. Plasma methionine concentrations should be monitored in patients with CBS deficiency *[See Warnings and Precautions (5.1)]*.

Dosages of up to 20 grams per day have been necessary to control homocysteine levels in some patients. However, one pharmacokinetic and pharmacodynamic *in vitro* simulation study indicated minimal benefit from exceeding a twice-daily dosing schedule and a 150 mg/kg/day dosage for Cystadane.

2.2 Administration

The prescribed amount of Cystadane should be measured with the measuring scoop provided (one level 1.7 mL 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.

3 DOSAGE FORMS AND STRENGTHS

Cystadane is a white, granular, hygroscopic powder for oral solution available in bottles containing 180 grams of betaine anhydrous.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypermethioninemia

Risk of Hypermethioninemia in Patients with CBS Deficiency

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 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.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

The most serious adverse reaction reported with Cystadane treatment is the development of hypermethioninemia and cerebral edema in patients with CBS Deficiency *[see Warnings and Precautions (5.1)]*.

The assessment of clinical adverse reactions is based on a survey study of 41 physicians, who treated a total of 111 homocystinuria patients with Cystadane. Adverse reactions were retrospectively recalled and were not collected systematically in this open-label, uncontrolled, physician survey. Thus, this list may not encompass all types of potential adverse reactions, reliably estimate their frequency, or establish a causal relationship to drug exposure. The following adverse reactions were reported (Table 1):

Table 1: Number of Patients with Adverse Reactions to Cystadane by Physician Survey

Adverse Reactions	Number of Patients
Nausea	2
Gastrointestinal distress	2
Diarrhea	1
“Bad Taste”	1
“Caused Odor”	1
Questionable psychological changes	1
“Aspirated the powder”	1

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Cystadane. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In postmarketing experience with Cystadane, severe cerebral edema and hypermethioninemia have been reported within 2 weeks to 6 months of starting betaine therapy, with complete recovery after discontinuation of Cystadane. All patients who developed cerebral edema had homocystinuria due to CBS deficiency and had severe elevation in plasma methionine levels (range 1,000 to 3,000 μM). As cerebral edema has also been reported in patients with hypermethioninemia, secondary hypermethioninemia due to betaine therapy has been postulated as a possible mechanism of action.

The following adverse reactions have been reported in patients during postmarketing use of Cystadane: anorexia, agitation, depression, irritability, personality disorder, sleep disturbed, dental disorders, diarrhea, glossitis, nausea, stomach discomfort, vomiting, hair loss, hives, skin odor abnormalities, and urinary incontinence.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

It is not known whether Cystadane is excreted in human milk. Use only if clearly needed.

8.4 Pediatric Use

The majority of case studies of homocystinuria patients treated with Cystadane have been pediatric patients, including patients ranging in age from 24 days to 17 years *[see Clinical Studies (14)]*. Children younger than 3 years of age may benefit from dose titration *[see Dosage and Administration (2)]*.

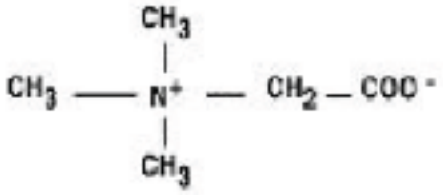
10 OVERDOSAGE

In an acute toxicology study in rats, death occurred frequently at doses equal to or greater than 10 g/kg.

11 DESCRIPTION

Cystadane (betaine anhydrous for oral solution) is an agent for the treatment of homocystinuria. It contains no ingredients other than anhydrous betaine. Cystadane is a white, granular, hygroscopic powder, which is diluted in water and administered orally. The chemical name of

betaine anhydrous powder is trimethylglycine. It has a molecular weight of 117.15. The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cystadane acts as a methyl group donor in the remethylation of homocysteine to methionine in patients with homocystinuria. Cystadane 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.

12.2 Pharmacodynamics

Cystadane was observed to lower plasma homocysteine levels in three types of homocystinuria, including CBS deficiency; MTHFR deficiency; and cbl defect. Patients have taken Cystadane for many years without evidence of tolerance. There has been no demonstrated correlation between Cystadane levels and homocysteine levels.

In CBS-deficient patients, large increases in methionine levels over baseline have been observed. Cystadane has also been demonstrated to increase low plasma methionine and Sadenosylmethionine (SAM) levels in patients with MTHFR deficiency and cbl defect.

12.3 Pharmacokinetics

Pharmacokinetic studies of Cystadane are not available. Plasma levels of Cystadane have not been measured in patients and have not been correlated to homocysteine levels.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity and fertility studies have not been conducted with Cystadane. No evidence of genotoxicity was demonstrated in the following tests: metaphase analysis of human lymphocytes; bacterial reverse mutation assay; and mouse micronucleus test.

14 CLINICAL STUDIES

Cystadane was studied in a double-blind, placebo-controlled, crossover study in 6 patients with CBS deficiency, ages 7 to 32 years at enrollment. Cystadane was administered at a dosage of 3 grams twice daily, for 12 months. Plasma homocystine levels were significantly reduced ($p<0.01$) compared to placebo. Plasma methionine levels were variable and not significantly different compared to placebo.

No adverse events were reported in any patient.

Cystadane has also been evaluated in observational studies without concurrent controls in patients with homocystinuria due to CBS deficiency, MTHFR deficiency, or cbl defect. A review of 16 case studies and the randomized controlled trial previously described was also conducted, and the data available for each study were summarized; however, no formal statistical analyses were performed. The studies included a total of 78 male and female patients with homocystinuria who were treated with Cystadane. This included 48 patients with CBS deficiency, 13 with MTHFR deficiency, and 11 with cbl defect, ranging in age from 24 days to 53 years. The majority of patients (n=48) received 6 gm/day, 3 patients received less than 6 gm/day, 12 patients received doses from 6 to 15 gm/day, and 5 patients received doses over 15 gm/day. Most patients were treated for more than 3 months (n=57) and 30 patients were treated for 1 year or longer (range 1 month to 11 years). Homocystine is formed nonenzymatically from two molecules of homocysteine, and both have been used to evaluate the effect of Cystadane in patients with homocystinuria. Plasma homocystine or homocysteine levels were reported numerically for 62 patients, and 61 of these patients showed decreases with Cystadane treatment. Homocystine decreased by 83-88% regardless of pre-treatment level, and homocysteine decreased by 71-83%, regardless of the pre-treatment level. Clinical improvement, such as improvement in seizures, or behavioral and cognitive functioning, was reported by the treating physicians in about three-fourths of patients. Many of these patients were also taking other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), and folate with variable biochemical responses. In most cases, adding Cystadane resulted in a further reduction of either homocystine or homocysteine.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 52276-400-01 180 g/bottle

16.1 Storage

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

17 PATIENT COUNSELING INFORMATION

Patients should be advised of the following information before beginning treatment with Cystadane:

17.1 Dosing and Administration

- Instruct patients and caregivers that Cystadane should only be taken as directed by their healthcare professional.
- Instruct patients and caregivers to administer Cystadane as follows:
- Shake bottle lightly before removing cap.
    - Measure with the scoop provided.

- Measure the number of scoops as prescribed by their healthcare professional. One level scoop (1.7 mL) is equivalent to 1 gram of betaine anhydrous powder.
- Mix powder with 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest mixture immediately.
- Always replace the cap tightly after using, and protect powder from moisture.

Supplied by:

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Puteaux, France

Licensed to and Distributed by:

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Lebanon, NJ 08833 U.S.A.

For drug or ordering information please call AnovoRx Group, LLC, Customer service at 1-888-487-4703.

CYSTADANE®
betaine anhydrous for oral solution

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