Living with

HOMOCYSTINURIA

caused by a cobalamin cofactor metabolism (cbl) defect

By maintaining good metabolic control, people with CBL DEFECTS may be able to prevent or reduce many symptoms or complications.

What are cobalamin cofactor metabolism defects?

Cobalamin cofactor metabolism defects, **also known as cbl defects**, are **rare inherited disorders** that affect the body's **metabolism**.

Cbl defects may cause a condition called homocystinuria

Many different cbl defects impair the body's ability to **metabolize, or break down,** an **amino acid called homocysteine**. Amino acids are building blocks that the body uses to make proteins. **The body makes homocysteine when it breaks down methionine**, another amino acid. Most foods contain methionine, particularly high-protein foods such as meat and eggs.

A condition called **homocystinuria** occurs when there is a **build-up of homocysteine in blood and urine**. Since too much homocysteine can harm the body, it needs to **convert some of the homocysteine back to methionine** with the help of **cobalamin, also known as vitamin B12**. The body gets cobalamin from foods. The body goes through **a series of steps** to convert cobalamin to a form of cobalamin that is needed to convert homocysteine back to methionine. If any step in this process does not happen as it should, then **homocysteine builds up and methionine decreases** in the body.

What are cobalamin cofactor metabolism defects?

Cbl defects may also cause a second condition called methylmalonic acidemia

In addition to impairing the body's ability to break down homocysteine, some cbl defects also impair the body's ability to **break down methylmalonic acid (MMA).**

A condition called **methylmalonic acidemia** occurs when there is a **build-up of MMA in blood and urine**. The body makes MMA when it breaks down protein. Just as too much homocysteine can harm the body, the same is true for MMA. The body goes through **a series of steps to convert cobalamin** that is obtained from foods to a form of cobalamin that is needed **to break down MMA**. If any step in this process does not happen as it should, then **MMA builds up** in the body.

There are many cbl defects

Each cbl defect is named with a different letter of the alphabet based on what gene is affected and where the breakdown in metabolism occurs. Cbl defects that cause only homocystinuria are known as single disorders. Cbl defects that cause both homocystinuria and methylmalonic acidemia are known as combined disorders.

Single Disorders

Homocystinuria

cblD defect (variant 1)

cblE defect

cblG defect

Combined Disorders

Homocystinuria and Methylmalonic Acidemia

cblC defect

cblD defect

cblF defect

cblJ defect

cblX defect

Cbl defects can affect health in many ways

High levels of homocysteine and methylmalonic acid can cause **serious health problems.** Many parts of the body may be affected. The symptoms below pertain to **cblC defect**, the **most common cbl defect**, but **other types of cbl defects may cause some of the same symptoms.**

BRAIN & SPINAL CORD

Drowsiness, floppy muscles and joints, and **developmental delays**, such as being slow to roll over or crawl, are common early symptoms in infants. **Mental health problems, muscle stiffness**, and an **unusual way of walking** may occur in individuals whose symptoms develop after infancy.

GROWTH & FEEDING

Feeding problems and **reduced growth** are common early symptoms in infants.

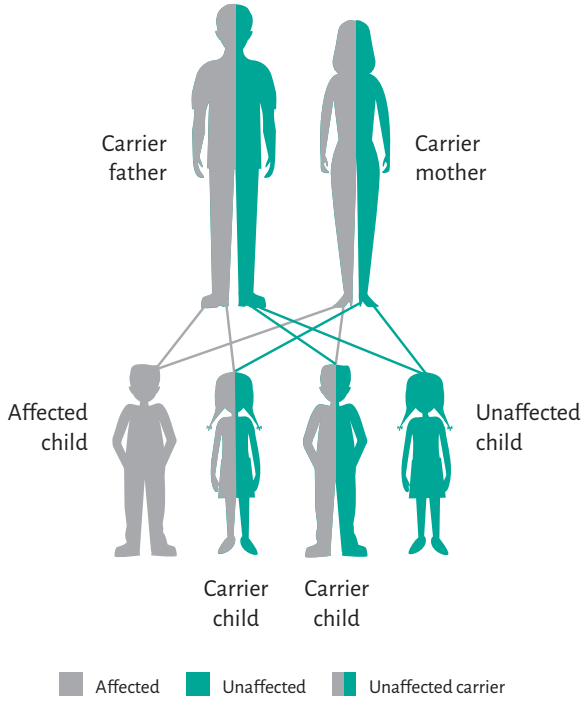
EYES

Unusual eye movements and **vision problems** are common early symptoms in infants.

HEART & BLOOD

Inherited heart disease, megaloblastic anemia, and **blood clots** are somewhat common early symptoms in infants. Individuals whose symptoms develop after infancy are also at risk for blood clots.

Diagnosing cbl defects



A person with a cbl defect (except for cblX defect) **has inherited two mutated copies of a specific gene – one from each parent.** People with one normal gene and one gene with a mutation are known as carriers. They do not have symptoms. When both parents are carriers, each child in the family has a 25% chance of having the disorder.

CblX defect is caused by a gene mutation on the X chromosome.

In the United States, **most states screen newborns for cblC and cblD defects**. However, newborn screening may not catch all newborns with the conditions. Some people with cbl defects are not diagnosed until after symptoms appear. A diagnosis can be made at any age since symptoms may develop at different times in different people.

The diagnosis is made through **blood tests measuring the levels of homocysteine, methionine, and methylmalonic acid. Genetic testing** can confirm the specific type of cbl defect.

Working with a healthcare team to prevent or reduce symptoms

Ideally, a person's healthcare team will include a **metabolic specialist** who is familiar with managing cbl defects. A metabolic specialist is a doctor who specializes in treating genetic conditions that involve the body's metabolism.

Other healthcare professionals, such as an ophthalmologist, a neurologist, a cardiologist, a hematologist, and physical and/or occupational therapists, may provide care as needed to help address symptoms.

The healthcare team will work with the affected individual and family to develop – and update over time – **a personalized treatment plan**.

The goal of treatment is to prevent or reduce symptoms or complications by keeping homocysteine, methionine, and methylmalonic acid levels in the blood as close to normal as possible.

Periodic blood tests are done to see how well someone's treatment plan is working and to adjust the plan as needed.

Taking medicines

What a personalized treatment plan may include:

- **Getting hydroxocobalamin injections** – Hydroxocobalamin is a form of vitamin B12 that helps keep levels of homocysteine and methylmalonic acid down and levels of methionine normal.
- **Taking CYSTADANE® (betaine anhydrous for oral solution)** – CYSTADANE is an FDA-approved prescription medicine that helps the body convert homocysteine back to methionine, lowering the levels of homocysteine in the blood.

Many parents get trained to give their child hydroxocobalamin injections. Home injections can become part of a child's routine. Injections are generally given daily at first, then less often if there is good metabolic control.

Indications and Usage

CYSTADANE® (betaine anhydrous for oral solution) is indicated in children and adults for the treatment of homocystinuria to decrease high homocysteine blood levels. Homocystinuria is a rare genetic disorder in which there is an abnormal accumulation of the amino acid homocysteine in the blood and urine.

The following are considered to be homocystinuria disorders:

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

Important Safety Information

- Hypermethioninemia in Patients with CBS Deficiency: CYSTADANE may worsen high methionine blood levels and accumulation of excess fluid in the brain has been reported. If you have been told you have CBS deficiency, your doctor will be monitoring your methionine blood levels to see if changes in your diet and dosage are necessary.
- Most common side effects were nausea and gastrointestinal distress, based on a survey of doctors.
- **To report SUSPECTED SIDE EFFECTS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

Please see accompanying Full Prescribing Information or visit www.Cystadane.com.

Find out more

To learn more about cbl defects, check out:

- **HCU Network America**, whose mission is to help patients with homocystinuria and related disorders manage their disease and to find a cure. **https://hcunetworkamerica.org**
- **Organic Acidemia Association**, which provides support and information for people with inherited metabolic disorders, including homocystinuria caused by several combined cbl defects. **https://www.oaanews.org/**

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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)

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

CYSTADANE is a methylating agent indicated in pediatric and adult patients for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations. 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

Adults and Pediatric Patients 3 Years of Age and Older

- The recommended dosage is 6 grams per day, administered orally in divided doses of 3 grams twice daily. (2.1)

Pediatric Patients Less than 3 Years of Age

- The recommended starting dosage is 100 mg/kg/day, administered orally in divided doses of 50 mg/kg twice daily, and then increased weekly by 50 mg/kg increments. (2.1)
- Monitor patient response by plasma homocysteine concentrations. (2.1)
- Increase the dosage gradually until the plasma total homocysteine concentration is undetectable or present only in small amounts. (2.1)

Preparation and Administration Instructions

- 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 until completely dissolved, or mixed with food for immediate ingestion. (2.2)

DOSAGE FORMS AND STRENGTHS

For oral solution: in bottles containing 180 grams of betaine anhydrous. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypermethioninemia in Patients with CBS Deficiency: CYSTADANE may worsen elevated plasma methionine concentrations and cerebral edema has been reported. Monitor plasma methionine concentrations in patients with CBS deficiency. Keep plasma methionine concentrations below 1,000 micromol/L through dietary modification and, if necessary, a reduction of CYSTADANE dosage. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (> 2%) are: nausea and gastrointestinal distress, based on physician survey. (6.1)

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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CYSTADANE® is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations in pediatric and adult patients. 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

Therapy with CYSTADANE should be directed by physicians knowledgeable in the management of patients with homocystinuria.

Adults and Pediatric Patients 3 Years of Age and Older

The recommended dosage is 6 grams per day, administered orally in divided doses of 3 grams twice daily.

Pediatric Patients Less than 3 Years of Age

The recommended starting dosage is 100 mg/kg/day divided in twice daily doses, and then increased weekly by 50 mg/kg increments.

Monitoring

Monitor patient response to CYSTADANE by homocysteine plasma concentration. Increase the dosage in all patients gradually until the plasma total homocysteine concentration is undetectable or present only in small amounts. An initial response in homocysteine plasma concentrations usually occurs within several days and steady state plasma concentrations occur within a month.

Monitor plasma methionine concentrations in patients with CBS deficiency *[See Warnings and Precautions (5.1)].*

Maximum Dosage

Dosages of up to 20 grams/day have been necessary to control homocysteine concentrations 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 Preparation and Administration Instructions

- Shake bottle lightly before removing cap.
- Measure the number of scoops for the patient's dose with the scoop provided. 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 the bottle from moisture.

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 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 *[see Adverse Reactions (6.2)].* Monitor plasma methionine concentrations in patients with CBS deficiency. Plasma methionine concentrations should be kept below 1,000 micromol/L through dietary modification and, if necessary, a reduction of CYSTADANE dosage.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Hypermethioninemia and cerebral edema in patients with CBS deficiency *[see Warnings and Precautions (5.1)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

Severe cerebral edema and hypermethioninemia have been reported within 2 weeks to 6 months of starting CYSTADANE 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 concentrations (range 1,000 to 3,000 microM). 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 *[see Warnings and Precautions (5.1)]*.

Other adverse reactions include: 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

Risk Summary

Available data from a limited number of published case reports and postmarketing experience with CYSTADANE use in pregnancy have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with betaine.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of betaine in human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CYSTADANE and any potential adverse effects on the breastfed child from CYSTADANE or from the underlying maternal condition.

8.4 Pediatric Use

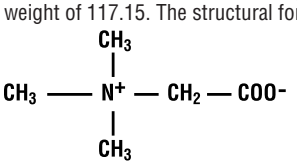
The safety and effectiveness of CYSTADANE have been established in pediatric patients. The majority of case studies of homocystinuria patients treated with CYSTADANE have been pediatric patients, including patients ranging in age from 24 days to 17 years *[see Clinical Studies (14)]*. Children younger than 3 years of age may benefit from dose titration *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

There is no information on CYSTADANE overdose in humans. 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. 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.

12.2 Pharmacodynamics

CYSTADANE was observed to lower plasma homocysteine concentrations 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 Betaine concentrations and homocysteine concentrations.

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

12.3 Pharmacokinetics

Pharmacokinetic studies of CYSTADANE are not available. Plasma betaine concentrations following administration of CYSTADANE have not been measured in patients and have not been correlated to homocysteine concentrations.

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 (3 males and 3 females) 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 concentrations were significantly reduced ($p<0.01$) compared to placebo. Plasma methionine concentrations were variable and not significantly different compared to placebo.

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 concentrations were reported numerically for 62 patients, and 61 of these patients showed decreases with CYSTADANE treatment. Homocystine decreased by 83 to 88% regardless of the pre-treatment concentration, and homocysteine decreased by 71 to 83%, regardless of the pre-treatment concentration. 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 concentrations.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 52276-400-01 180 g/bottle

Storage

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

17 PATIENT COUNSELING INFORMATION

Preparation and Administration Instructions

Instruct patients and caregivers to administer CYSTADANE as follows:

- Shake bottle lightly before removing cap.
- Measure the number of scoops for the patient's dose with the scoop provided. 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 bottle from moisture.

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CYSTADANE®
betaine anhydrous for oral solution

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