

Living with

■ CLASSICAL HOMOCYSTINURIA: The basics



CLASSICAL HOMOCYSTINURIA IS
A LIFELONG DISORDER. BUT BY KEEPING
HOMOCYSTEINE LEVELS AS CLOSE TO NORMAL
AS POSSIBLE, PEOPLE WITH CLASSICAL
HOMOCYSTINURIA MAY BE ABLE TO PREVENT OR
REDUCE MANY SYMPTOMS OR COMPLICATIONS.

WHAT IS CLASSICAL HOMOCYSTINURIA?

There are three types of genetic disorders that cause homocystinuria. Each type has a different cause and different health issues. This brochure will talk about **classical homocystinuria**.

Classical homocystinuria is a **rare inherited disorder** that impairs 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 some methionine. But high-protein foods such as meat, fish, eggs, or cheese tend to have the most methionine. Plant-based foods such as beans, tofu, and nuts also have higher amounts of methionine. So when you eat these types of foods, more methionine enters your body.

Another name for classical homocystinuria is **CBS deficiency**. CBS stands for **cystathionine beta-synthase**. CBS is an **enzyme** that helps the body break down homocysteine. If there is not enough CBS enzyme activity, **homocysteine builds up in blood and urine**, resulting in **homocystinuria**. This can cause serious health problems.

Different types of classical homocystinuria

There are three different types of classical homocystinuria:

- **Vitamin B6-responsive**
- **Partially vitamin B6-responsive**
- **Vitamin B6-non-responsive**

A test called a **vitamin B6 challenge** can determine which type of classical homocystinuria a person has. The purpose is to find out how someone responds to vitamin B6.

If someone's body is making enough CBS enzyme, then vitamin B6 may help the CBS enzyme do its job. If their body is not making enough CBS enzyme, then vitamin B6 probably won't help.

Knowing what type of classical homocystinuria a person has will help the healthcare team develop a treatment plan.

CLASSICAL HOMOCYSTINURIA CAN AFFECT HEALTH IN MANY WAYS

High blood homocysteine levels can be harmful to the body, mainly in four areas: brain, eyes, bones, and blood.



BRAIN

Learning problems and **developmental delays**, such as being slow to roll over, sit up, walk, or talk, are common early symptoms in children. **Seizures** and **behavioral problems**, such as anxiety and depression, may also occur.



EYES

Nearsightedness (difficulty seeing things at a distance) and **dislocation of the lens** of the eye are common early symptoms in children. **Quivering of the iris** (the colored part of the eye) and **glaucoma** (increased pressure in the eye) may also occur.



BONES

As children with classical homocystinuria continue to grow, their **bones may grow longer than normal** so that they may be tall with long arms, legs, fingers, and toes. They are also more likely to develop **scoliosis** (curved spine) and **osteoporosis** (brittle or weak bones).



BLOOD

Classical homocystinuria increases a person's risk of developing **blood clots** in the arms, legs, lungs, or brain.



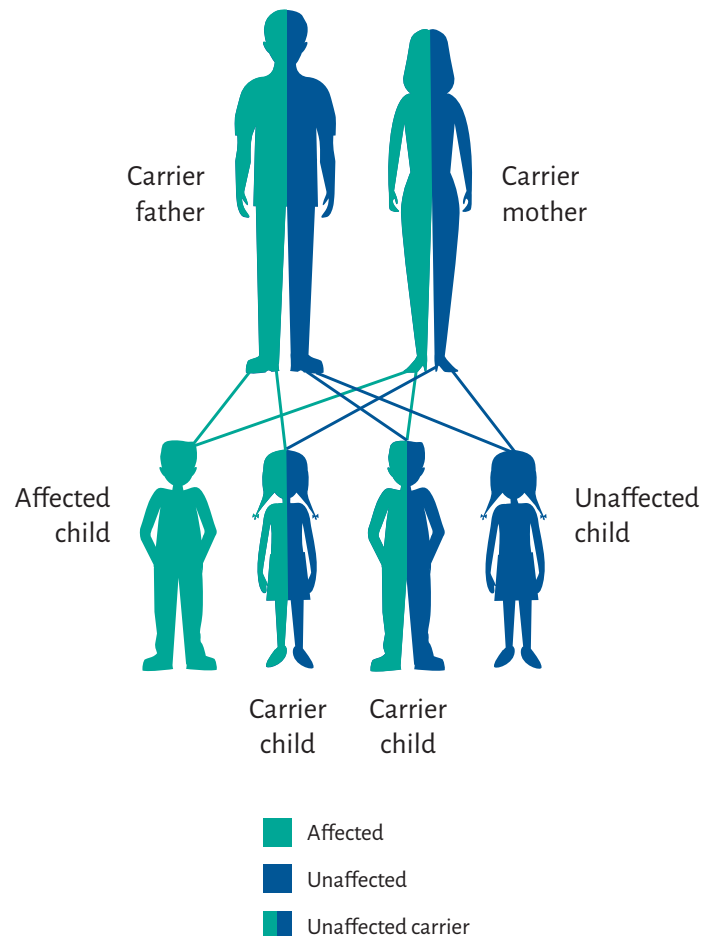
CLASSICAL HOMOCYSTINURIA IS A GENETIC DISORDER

A person with classical homocystinuria has inherited two *CBS* genes with mutations – 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.

Diagnosing classical homocystinuria

All newborns in the United States are **screened** for classical homocystinuria. However, newborn screening may not catch all newborns with the condition. Some people are not diagnosed until after symptoms appear. A diagnosis may be provided at any age since symptoms may develop at different times in different people.

The diagnosis is confirmed by **blood tests measuring the levels of homocysteine and methionine** and/or by **genetic testing**. Other blood tests may be done to help guide treatment.



WORKING WITH A HEALTHCARE TEAM

Ideally, a person's healthcare team will include a **metabolic specialist** who is familiar with managing classical homocystinuria. A metabolic specialist is a doctor who specializes in treating genetic conditions that involve the body's metabolism, which is all the physical and chemical processes that occur in cells to maintain life.

Most centers that treat metabolic disorders have a **metabolic dietitian** on staff to help people whose conditions require special diets.

Other healthcare professionals, such as an ophthalmologist, a hematologist, an orthopedist,



a cardiologist, and a neurologist, 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**.



A PERSONALIZED TREATMENT PLAN TO PREVENT OR REDUCE SYMPTOMS

A **personalized treatment plan** for classical homocystinuria may include one or more of the following:

- **Taking vitamin B6 supplements**, which help the CBS enzyme break down homocysteine. Some people respond very well to vitamin B6, while others do not. **Other B vitamin supplements** may also be part of the plan.
- **Eating a low-protein diet**, developed with help from a **metabolic dietitian**, to limit methionine in the diet.
- **Taking a methionine-free formula** to get needed essential amino acids while on a low-protein diet.
- **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.
- **Taking other medicines to help prevent certain complications, such as blood clots.**

The goal of treatment is to prevent or lessen further damage to the body by keeping homocysteine levels as close to normal as possible. Periodic blood tests to measure homocysteine levels are done to see how well someone's treatment plan is working and to adjust their plan as needed.



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.

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

To learn more about classical homocystinuria, check out:

HCU Network America, whose mission is to help patients with HCU and related disorders manage their disease and to find a cure. <https://hcunetworkamerica.org/>

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)

FULL PRESCRIBING INFORMATION: CONTENTS*

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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.

- 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

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

- 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

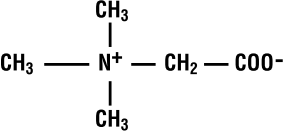
The safety and effectiveness of CYSTADANE have been established in pediatric patients. The majority of case studies of homocystinuria patients treated with CYSTADANE have been pediatric patients, including patients ranging in age from 24 days to 17 years [see Clinical Studies (14)]. Children younger 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 homocysteine 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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betaine anhydrous for oral solution

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