Living with a

Cobalamin Cofactor

Metabolism Defect

This brochure will help you understand the different types of cobalamin cofactor metabolism defects that cause homocystinuria, how they affect your body, and how you can manage your condition

A few words about this brochure

Has your doctor diagnosed you or your child with a **cobalamin** (co-BAL-uh-min) **cofactor metabolism defect**? Cobalamin cofactor metabolism defects are one of three types of genetic disorders that cause **homocystinuria** (HO-mo-SIS-tin-YUR-ee-uh). The information in this brochure will help you understand these defects and how you can manage your condition.

You may be reading this brochure because you have a cobalamin cofactor metabolism defect or because your child or a sibling or a friend has one. Or perhaps you're a healthcare professional. Please note the brochure addresses "you," but it's understood that "you," the reader, may not have a cobalamin cofactor metabolism defect yourself.

For the remainder of this brochure, cobalamin (cbl) cofactor metabolism defects will be referred to as **cbl defects**.

What is homocystinuria?

You may have heard the word "homocystinuria" for the first time when your doctor talked to you about possibly having a cbl defect. **Homocystinuria caused by cbl defects** is the name for a group of rare disorders involving the **amino acid homocysteine** (HO-mo-SIS-teen). Amino acids are building blocks that your body uses to make proteins. Homocystinuria occurs when there is a buildup of homocysteine in your blood and urine. High levels of homocysteine can be harmful to your body.

How does homocysteine get in your body?

It starts with the foods you eat. Your body makes homocysteine from another amino acid called **methionine** (meh-THIGH-uh-neen). 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. Then your body breaks down – or metabolizes – the methionine you've eaten into homocysteine.

How do cbl defects cause homocystinuria?

Since too much homocysteine can harm your body, it needs to convert some of the homocysteine back to methionine. This process involves **cobalamin – also called vitamin B12**—that you get from the foods you eat. Your body goes through a series of steps to convert vitamin B12 into **methylcobalamin** (MEH-thul-co-BAL-uh-min). This is the form of cobalamin that your body needs to convert homocysteine back to methionine.

When the process is working the way it should, your body uses methylcobalamin and a few **enzymes** to convert homocysteine back to methionine. Enzymes are proteins that help chemical reactions take place in the body.

However, the process can break down if:

- Your body cannot successfully complete the steps to produce enough methylcobalamin.
- Your body cannot produce the enzymes it needs for the chemical reaction to occur, or your body makes enzymes that do not work properly.

Why would this happen? Your body uses many genes to convert cobalamin to methylcobalamin and to make the enzymes that are needed to complete this process. If something is wrong with any of these genes, then the process can break down.

If any step in the process does not occur, then your body cannot convert homocysteine back to methionine through this pathway. This causes homocysteine to build up in your body. It also causes methionine to decrease. Both can lead to serious health problems.

Are there different types of cbl defects?

Yes – there are many types of cbl defects. Each type is named with a different letter of the alphabet. The type of cbl defect you have depends on what gene is affected and where the process breaks down. Some cbl defects also cause a second disorder along with homocystinuria. These are called "combined disorders."

Combined disorders

Combined disorders occur in people who cannot successfully complete the steps to produce enough methylcobalamin and also a second form of cobalamin that your body needs. These disorders are known as: **cblC defect** (**cblC**), **cblD defect** (**cblD**), **cblF defect** (**cblF**), **cblJ defect** (**cblJ**), and **cblX defect** (**cblX**).

When your body undergoes the steps to make methylcobalamin, it uses many of the same steps to help make a second type of cobalamin called **adenosylcobalamin** (uh-DEEN-oh-sil-co-BAL-uh-min). When your body does not produce enough adenosylcobalamin, a certain enzyme reaction cannot take place. This results in the buildup of a substance called **methylmalonic** (MEH-thul-muh-LON-ik) **acid** (**MMA**) that your body makes when it digests protein. High levels of MMA in your blood can cause harmful symptoms to develop. This condition is called **methylmalonic acidemia**.

Individuals who have a combined disorder have both homocystinuria and methylmalonic acidemia. Both disorders can cause serious health problems.

CblC defect is the most common cbl defect. About 1 in every 100,000 babies is born with cblC defect in the United States.

Are there different types of cbl defects?

Single disorders

Homocystinuria without methylmalonic acidemia occurs when a person's body cannot complete the final steps in the process to produce methylcobalamin, or a person's body does not properly produce an enzyme that is needed to interact with methylcobalamin. These disorders are known as: **cblD defect variant 1** (**cblD variant 1**), **cblE defect** (**cblE**), and **cblG defect** (**cblG**).

Methylmalonic acidemia without homocystinuria occurs when a person does not produce enough adenosylcobalamin. These disorders are known as: **cblA defect** (**cblA**), **cblB defect** (**cblB**), and **cblD defect variant 2** (**cblD variant 2**). These cbl defects will not be covered any further in this brochure.

The different types of cbl defects affect the body in different ways and can lead to different symptoms. Knowing the type of cbl defect you have is important for developing a treatment plan that will help you manage homocysteine, methionine, and methylmalonic acid (MMA) levels in your body on a day-to-day basis.

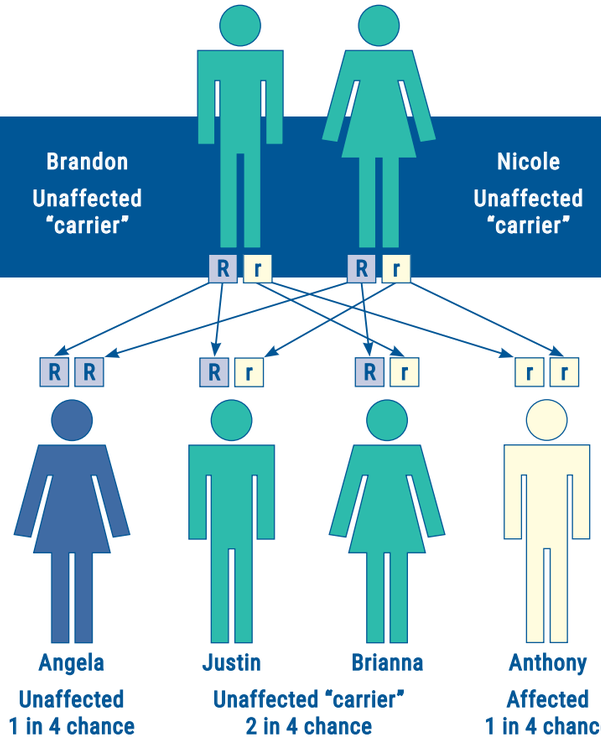
Why do you have a cbl defect?

Cbl defects are **genetic disorders**, which is another way of saying that the conditions are inherited from your parents. How you inherited your disorder depends on the specific type of cbl defect you have. Since homocystinuria due to cbl defects is caused by genetics, it is a lifelong condition.

Inheritance pattern for all cbl defects except cblX

Cbl defects (except cblX) occur when you inherit two copies of an abnormal variation of a specific gene, one from each parent. The medical term for this kind of inheritance is **autosomal recessive**.

If you have homocystinuria due to a cbl defect and your parents do not, then they are **carriers** of the condition. This means they have one normal copy and one abnormal variation of the affected gene. They don't have homocystinuria because their normal copy of the gene is able to keep their homocysteine levels at normal levels.



As an example, this diagram shows how homocystinuria due to cblC defect may affect families. CblC defect is due to an abnormal variation in a **gene called *MMACHC***. This gene helps convert vitamin B12 that you get from the foods you eat into methylcobalamin, the form of cobalamin that your body needs.

In this family, the parents, Brandon and Nicole, are carriers of cblC defect. Each child in the family has a 1 in 4 chance of having cblC defect. In this case, Anthony, their son, has cblC defect because he inherited two abnormal variations of the *MMACHC* gene. The other children – Brianna, Justin, and Angela – do not have cblC defect. But Brianna and Justin are carriers of the defect because they have one normal copy and one abnormal variation of the *MMACHC* gene.

Both of them could potentially pass on the affected gene to their future children. Angela has two normal copies of the gene. She will pass on a normal copy of the gene to any future children that she has.

Being a carrier of homocystinuria due to cblC defect is much more common than having the condition. That's why many people who are diagnosed with cblC defect have no known family history of homocystinuria or methylmalonic acidemia.

Why do you have a cbl defect?

Inheritance pattern for cblX defect

CblX defect is caused by an abnormal variation in the ***HCFC1* gene**, which is located on the **X chromosome**. CblX defect follows **X-linked recessive inheritance** in families. X-linked genes affect males and females differently.

Males have one X and one Y chromosome. If a male inherits an abnormal *HCFC1* gene on the X chromosome from his mother, then he will have cblX defect. He cannot inherit cblX defect from his father, even if his father has cblX defect, since he inherits a Y chromosome from his father.

Females have two X chromosomes. If a female inherits two abnormal *HCFC1* genes, one from each parent, then she will have cblX defect. However, if a female inherits only one abnormal gene on the X chromosome from either her mother or her father, then she is a **carrier** of the condition. She is not likely to have any symptoms of the disorder, or if she does, they are not likely to be severe. This is because her second copy of the *HCFC1* gene is usually working the way it should.

How and when are cobalamin defects diagnosed?

Homocystinuria caused by cbl defects is diagnosed by lab tests that measure the blood levels of:

- Homocysteine – usually higher than normal in all cbl defects
- Methionine – usually lower than normal in all cbl defects
- Methylmalonic acid – usually higher than normal in all combined disorders

Your doctor may also suggest more blood testing to identify the specific gene that's causing your cbl defect. This is known as "DNA sequencing," and it's done by a special lab. Because many cbl defects share similar blood test results, gene "panel" testing is done to assess many relevant genes at the same time. This type of genetic testing can confirm the diagnosis.

In the United States, most states screen newborns for cbl defects with combined homocystinuria and methylmalonic acidemia, such as cblC and cblD, by looking for markers in the blood caused by high levels of methylmalonic acid (MMA). A positive newborn screening will lead to diagnostic lab testing.

If the newborn screening test result is positive, then your doctor will order more testing to confirm the result. Newborn screening is not perfect and may not catch all newborns with the condition. Some babies who are born early (premature) may not be developed enough for the screening to be accurate.

Some people are not diagnosed with a cbl defect until after symptoms appear. Symptoms may develop at different times for different people, so diagnosis can occur at any age. And because cbl defects are rare, some doctors may not recognize the symptoms right away and the diagnosis can be delayed.

If you have homocystinuria due to a cbl defect, you were born with the disorder, even if you didn't have symptoms right away.

How can a cbl defect affect your health?

Different cbl defects can affect health in different ways. The symptoms you develop – or may be at risk of developing – depend on where in the homocysteine-to-methionine conversion process the error is occurring and whether you have a single or combined disorder. Symptoms may affect your brain and change how you think, move, and act. Symptoms may also affect other parts of your body, such as your eyes, heart, lungs, and bone marrow. Symptoms may vary, depending on what age they develop, and they can range from mild to severe.

Combined disorders

If you have a combined disorder, you have both homocystinuria and methylmalonic acidemia. Since cblC is the most common cbl defect, more is known about this disorder.

Early-onset form of cblC defect

Most people with cblC defect develop signs and symptoms before they are a year old. This is the "early-onset" form of cblC defect. Vision symptoms are common and may appear as early as several weeks after birth. Symptoms may include "wandering" eye movements, repetitive, uncontrolled eye movements, and lack of ability to fixate on things. These symptoms may lead to vision loss and problems with depth perception, balance, and coordination. In some children, vision problems may become severe. Other symptoms that affect different parts of the body may also develop – some very early, and some later in life.

Medical problems that may occur in individuals with early-onset form of cbIC defect

Physical symptoms related to the brain and spinal cord

- Small head and brain size (microcephaly)
- Buildup of fluid in the brain (hydrocephaly)
- Seizures
- Drowsiness or lack of energy
- Low muscle tone (floppy muscles and joints)

Eating/feeding

- Acting fussy and not wanting to nurse or take a bottle
- Failure to grow and gain weight as expected

Blood/heart/lungs/kidneys

- Anemia (problems with red blood cells)
- Heart disease
- Blood clots
- Kidney problems (damaged red blood cells cause blockages in kidneys and prevent them from functioning properly)

Eyes

- Rapid, uncontrolled, or wandering/scanning eye movements
- Visual impairment

Learning ability or performance

- Developmental delay or disability, such as slow to sit up, walk, or talk

People with other combined disorders may have some of the same symptoms. Doctors are still learning about the full range of symptoms.

How can a cbI defect affect your health?

Late-onset form of cbIC defect

People with a milder form of cblC defect may not develop symptoms until later in life – from childhood to adulthood. This is the "late-onset" form of cblC defect. It is less common than the early-onset form.

Medical problems that may occur in individuals with late-onset form of cbIC defect

- Blood clots
- Abnormal walking
- Muscle stiffness
- Learning problems
- Mental health problems

Eye problems that are common in babies and young children with cblC defect are less likely to occur in people with a milder form of cblC defect.

Single disorders

If you have cblD (variant 1), cblE, or cblG defect, then you have homocystinuria without methylmalonic acidemia. These cbl defects are very rare, and more is being learned as more people are being diagnosed.

Medical problems that may occur in individuals with cbID (variant 1), cbIE, or cbIG defects

These conditions tend to cause some of the same symptoms as cblC defect. Symptoms may include:

- Failure to grow and gain weight as expected
- Seizures
- Developmental delays
- Vision problems
- Movement or muscle problems
- Problems with red blood cells (anemia)

How can cbl defects be managed?

Learning from your doctor that you have a cbl defect may be unsettling for you and your family. But even though cbl defects are rare, there is knowledge about how to treat them, especially cblC defect.

Ideally you should be treated by 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. Some conditions are so rare that your metabolic specialist may need to consult with another specialist who has experience treating a particular condition.

Your healthcare team will develop a **treatment plan** based on your needs. Your treatment plan may include certain vitamins and medicines. You should work closely with the team to develop your plan.

The goal of treatment is to prevent or reduce symptoms or complications by keeping homocysteine, methionine, and methylmalonic acid (MMA) levels in your body as close to normal as possible. Your doctor may say that your goal is to have "good metabolic control."

A low-protein diet is often needed for people who have a different type of homocystinuria called classical homocystinuria. However, a low-protein diet also reduces methionine, which is usually already lower than normal if you have a cbl defect. Because low methionine levels can be harmful to the body, a low-protein diet is not recommended for people with cblC defect.

What vitamins or medicines may be helpful for cbl defects?

Hydroxocobalamin injections

Vitamin B12 or cobalamin plays a key role in helping to control homocysteine and methylmalonic acid (MMA) levels, so **hydroxocobalamin** injections are an important part of treatment for people with cbl defects.

Hydroxocobalamin is the only form of vitamin B12 that has been found to be effective. It must be given as injections and not taken by mouth. These injections help your body make methylcobalamin and adenosylcobalamin, which helps keep levels of homocysteine and MMA down and levels of methionine normal.

Hydroxocobalamin is generally given daily at first, then less often if you have good metabolic control.

Hydroxocobalamin is usually given by self-injections – giving yourself or your child injections at home. At first you might feel nervous or unsure about the idea, but many people, such as individuals with diabetes, learn to give themselves injections.

Your treatment team can train you so that you know how to:

- Clean injection sites
- Give injections
- Rotate injection sites to different parts of the body on different days

What vitamins or medicines may be helpful for cbl defects?

CYSTADANE® (betaine anhydrous for oral solution)

CYSTADANE is a prescription medicine that provides a different "pathway" in your body to convert homocysteine back to methionine, lowering the levels of homocysteine in your blood. CYSTADANE is powdered betaine. Betaine is produced naturally in the body. Some foods, such as beets, spinach, and some cereals, also contain tiny amounts of betaine.

Your doctor may add CYSTADANE to your treatment plan to help lower homocysteine blood levels. The most common side effects of CYSTADANE are nausea and gastrointestinal distress, based on a survey of doctors.

Hydroxocobalamin and CYSTADANE may work together to lower homocysteine blood levels and increase methionine blood levels.

Other therapies

Your doctor may add other therapies to your treatment plan, including carnitine (a chemical made from two amino acids), folate or folinic acid (vitamin B9) and methionine. However, it is unknown how much these and other treatments may help.

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 Prescribing Information.

Why is it important to follow your treatment plan?

Losing control of blood homocysteine, methionine, and methylmalonic acid (MMA) levels at any age may lead to serious health problems. Having good metabolic control may reduce or even prevent some complications.

For individuals with cblC defect, appropriate treatment may reduce or, in some cases, prevent complications, such as:

- Failure to grow and gain weight as expected
- The buildup of fluid in the brain (hydrocephalus)
- Kidney problems
- Blood disorders, such as blood clots

However, treatment may not be effective in preventing, delaying, or controlling vision problems.

For individuals with other types of cbl defects, the effects of treatment are not as well established since the conditions are so rare and less is known about them.

Research does show that for people with homocystinuria due to **cblE or cblG defects**, some problems, such as anemia and impaired thinking or reasoning skills, may respond to treatment.

What are some good ways to meet the challenges caused by cbl defects?

There are many things you can do to meet the challenges of living with a cbl defect. Working well with your healthcare team is very important. Here are things you can do that may help you get the most out of your doctor visits:

- **See your doctor regularly to check your blood homocysteine, methionine, and (if relevant) methylmalonic acid (MMA) levels.** Your blood test results will allow your doctor to see how well your treatment plan is working and to adjust you plan as necessary.
- **See other doctors as needed.** Your overall health, development, and well-being are very important. And as someone with a cbl defect, you'll have added needs. Doctors will be on the lookout for problems that can result from your type of cbl defect.

Here are more things you can do for yourself and your family:

- **Follow your treatment plan – every day!** The goal of your plan is to keep the levels of homocysteine, methionine, and methylmalonic acid (MMA) in your blood as close to normal as possible. By following your plan, you may be able to **prevent or lessen further damage** to areas of your body that are affected by your cbl defect.
- **Develop a routine to give B12 injections at home**, and follow your treatment team's instructions.
- **Find additional information and support** through patient advocacy organizations.
- **Be your own best advocate** by following your instincts and doing your own research if something doesn't seem quite right. But always talk to your doctor and healthcare team before making any changes to your treatment plan.
- **Encourage family members** to talk to their doctors about **getting tested** for the type of cbl defect you have. Early diagnosis and lifelong treatment are the best ways to prevent complications. Also encourage family members to get tested to see if they are carriers. A confirmed carrier may also want to find out if their partner is a carrier, too, so that they can best plan for their family's future.

What resources provide information about homocystinuria due to cbl defects?

These organizations provide information about homocystinuria due to cbl defects:

- **HCU Network America** – The mission of HCU Network America is to help people with homocystinuria (HCU) and related disorders manage their disease and to find a cure.
- **HCU Network Australia** – The aims of HCU Network Australia are to provide support and education for people affected by homocystinuria, improve diagnosis to enable appropriate treatment, and support clinical research.
- **EHOD – European Network and Registry for Homocystinurias and Methylation Defects** – The aim of E-HOD is to improve the health of people affected with homocystinurias and methylation defects by developing a patient registry, developing diagnostic and clinical care protocols, and evaluating newborn screening programs.
- **Organic Acidemia Association** – This patient advocacy organization provides support and information for people with inherited metabolic disorders. Homocystinuria caused by several cbl defects—cblC, cblD cblF, cblJ, and cblX—is included as part of the group's advocacy activities.

Thank you to Dr. James Weisfeld-Adams for his contributions to the development and review of this brochure.

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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.

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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.
- 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

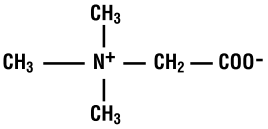
The safety and effectiveness of CYSTADANE have been established in pediatric patients. The majority of case studies of homocystinuria patients treated with CYSTADANE have been pediatric patients, including patients ranging in age from 24 days to 17 years *[see Clinical Studies (14)]*. Children younger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

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