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.
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.

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

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?
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 cblI 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.

**INHERITANCE PATTERN FOR cblX DEFECT**
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.

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.
How can a cbl defect affect your health?

Medical problems that may occur in individuals with early-onset form of cblC 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.

Late-onset form of cblC 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 cblC 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 cblD (variant 1), cblE, or cblG 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)
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.

How can cbl defects be managed?

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.

What vitamins or medicines may be helpful for cbl defects?

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
**OTHER THERAPIES**

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

**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.

**WHAT VITAMINS OR MEDICINES MAY BE HELPFUL FOR cbl DEFECTS?**
**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.

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**Why is it important to follow your treatment plan?**

Losing control of blood 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.

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**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 your 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.
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 aim 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 Methylolation 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—cblA, cblB, cblD, cblF, 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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**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

**DOSE AND ADMINISTRATION**

**Adults and Pediatric Patients 3 Years of Age and Older**

- 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.
- Monitor patient response by plasma homocysteine concentrations.

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

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**INDICATIONS AND USAGE**

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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.

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 63 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 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 63 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.

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.

Recordati Rare Diseases

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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