This brochure will help you understand what classical homocystinuria is, how it affects your body, and how you can manage your condition.
A FEW WORDS ABOUT THIS BROCHURE

Has your doctor diagnosed you or your child with homocystinuria (HO-mo-SIS-tin-YUR-ee-uh)? 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. The information will help you understand classical homocystinuria and how you can manage your condition.

You may be reading this brochure because you have classical homocystinuria or because your child or a sibling or a friend has it. Or perhaps you’re a healthcare professional. Please note the brochure addresses “you,” but it’s understood that “you,” the reader, may not have classical homocystinuria yourself.

WHAT IS HOMOCYSTINURIA?

You may have heard the word “homocystinuria” for the first time when your doctor talked to you about possibly having this condition. Homocystinuria is a rare disorder 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 the amino acid homocysteine in your blood and urine. High levels of homocysteine can be harmful to your body.

WHY IS THERE HOMOCYSTEINE IN YOUR BODY?

It starts with the foods you eat. Your body makes homocysteine from another amino acid called methionine (meh-THIGH-uh-teen). 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.
You have classical homocystinuria if you have an abnormal variation of the CBS (cystathionine beta-synthase) gene. The job of the CBS gene is to make CBS enzyme. This enzyme helps your body break down homocysteine into cysteine, another amino acid that your body needs. If you have classical homocystinuria, your CBS gene makes too little CBS enzyme or none at all, or it makes CBS enzyme that does not work properly. Without enough CBS enzyme activity, your body cannot break down enough homocysteine to keep homocysteine levels within the normal range. So homocysteine levels build up in your body, which can cause serious health problems.

**Classical homocystinuria** is a genetic condition, which is another way of saying you inherited it from your parents. Classical homocystinuria occurs when you inherit two copies of an abnormal variation of the CBS gene, one from each parent. (The medical term for this kind of inheritance is *autosomal recessive.*) Since classical homocystinuria is caused by genetics, it is a lifelong condition.

If you have classical homocystinuria, you were born with it, even if you didn’t have symptoms right away.

**Other names for classical homocystinuria are CBS deficiency and homocystinuria caused by CBS deficiency.**

If you have classical homocystinuria 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 CBS gene. They don’t have classical homocystinuria because their normal copy of the CBS gene produces enough of the CBS enzyme to keep homocysteine levels at normal levels.

This diagram shows how classical homocystinuria may affect families. In this family, the parents, Jason and Danielle, are carriers of classical homocystinuria. Each child in the family has a 1 in 4 chance of having classical homocystinuria. In this case, James, their son, has the condition because he inherited two abnormal variations of the CBS gene. The other children – Jennifer, Brady, and Kayla – do not have classical homocystinuria. But Jennifer and Brady are carriers of the condition because they have one normal copy and one abnormal variation of the CBS gene.

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

Being a carrier of classical homocystinuria is much more common than having the condition. That’s why many people who are diagnosed with classical homocystinuria have no known family history of the condition.
Your doctor will order blood tests to determine if you have classical homocystinuria. If the results show high levels of homocysteine and methionine in your blood, then most likely you have classical homocystinuria. Your doctor may also suggest more blood testing to identify the variation in your CBS gene. This is known as “DNA sequencing,” and it’s done by a special lab. Genetic testing can confirm a diagnosis of classical homocystinuria.

In the United States, every state screens newborns for classical homocystinuria. The screening test measures blood levels of methionine. 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. In some newborns, the level of methionine may not be high enough at the time of the screening test to trigger a positive result. Also, some babies who are born early (premature) may not be developed enough for the screening to be accurate.

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

"Until I was diagnosed with homocystinuria at age 54, the doctors thought I had Marfan syndrome. When I was around 2 years old, I developed dislocated lenses so I had to start wearing really thick glasses. In high school, I developed scoliosis so I had to wear a back brace 23 hours a day for over a year. I wasn’t allowed to participate in PE because of my back. Years later I started having trouble with blood clots, and at age 46 I had a stroke."

— Pam P., person living with classical homocystinuria

Your doctor will need to do another test to determine which type of classical homocystinuria you have. This test is called a vitamin B6 challenge or a pyridoxine challenge. The purpose is to find out how you will respond to vitamin B6.

If your body is making enough CBS enzyme, then vitamin B6 – also called pyridoxine – may help the CBS enzyme do its job. If your body is not making enough CBS enzyme, then vitamin B6 probably won’t help.

It is important for your doctor to know what type of classical homocystinuria you have in order to develop the right treatment plan for you.

The results from your CBS gene testing may suggest whether you will be vitamin B6-responsive, but the only way to know for sure is to do the vitamin B6 challenge test.

"Samantha had an abnormal newborn screening, and a month or two later a genetic test confirmed her homocystinuria diagnosis. She started treatment right away. She’s 2 now, and she’s doing really well. She hasn’t had any symptoms."

— Amber G., mother of Samantha, who has classical homocystinuria
Test results

<table>
<thead>
<tr>
<th>Vitamin B6-responsive or pyridoxine-responsive</th>
<th>Partially vitamin B6-responsive or partially pyridoxine-responsive</th>
<th>Vitamin B6-non-responsive or pyridoxine-non-responsive</th>
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<tbody>
<tr>
<td>If the levels of homocysteine and methionine are greatly reduced with the use of vitamin B6, then you are vitamin B6-responsive or pyridoxine-responsive.</td>
<td>If the levels of homocysteine and methionine are somewhat reduced with the use of vitamin B6, then you are partially vitamin B6-responsive or partially pyridoxine-responsive.</td>
<td>If the levels of homocysteine and methionine in your blood are not reduced with the use of vitamin B6, then you are vitamin B6-non-responsive or pyridoxine-non-responsive.</td>
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How can classical homocystinuria affect your health?

High homocysteine levels can be harmful to your body, mainly in four areas: brain, eyes, bones, and blood. Complications in each of these areas may include:

**Brain:**
- Learning problems and developmental delays, such as being slow to sit up, walk, or talk – common early symptoms in children
- Behavioral problems, such as anxiety and depression
- Seizures
- Increased risk of strokes (from blood clots developing in the brain or traveling to the brain)

**Eyes:**
- Near-sightedness (often severe) – a common and early symptom in children
- Lens dislocation – a common and early symptom in children
- Quivering of the iris (the colored part of the eye)
- Increased pressure in the eye (glaucoma)

**Bones:**
- Bones that grow longer than normal, for example, tall body with long arms, legs, fingers, and toes
- Abnormally curved spine (scoliosis)
- Brittle or weak bones (osteoporosis)

**Blood:**
- Development of blood clots in veins or arteries that can obstruct blood flow. These may occur in the arms, legs, brain (resulting in stroke), or lungs (resulting in pulmonary embolism)

The medical term for a blood clot is thrombus. When a blood clot breaks off and travels through the bloodstream to another part of the body, the medical term is thromboembolism.
How can classical homocystinuria be managed?

Hearing from your doctor that you have classical homocystinuria may be unsettling for you and your family. But even though classical homocystinuria is a rare disorder, a lot is known about how to treat it.

Ideally you should be treated by 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. Most centers that treat metabolic disorders have specialist dietitians on staff to help people whose conditions require special diets. Your healthcare team will develop a treatment plan based on your needs. 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 levels in your body as close to normal as possible. Your doctor may use the words, “achieving your target blood homocysteine levels.”

“What vitamins may be helpful for classical homocystinuria?

Vitamin B6 (pyridoxine) supplements

Vitamin B6 is a “helper” in the body. It plays a key role in helping the CBS enzyme break down homocysteine. So vitamin B6 supplements can be an important part of therapy for some people with classical homocystinuria.

If you have B6-responsive classical homocystinuria, then you may be able to lower and maintain your target homocysteine levels with vitamin B6 supplements alone.

If you have either B6-non-responsive or partially vitamin B6-responsive classical homocystinuria, then vitamin B6 supplements will not lower your homocysteine levels enough, and you will need other therapies.

Additional B vitamin supplements

Other B vitamins – B12 and folate – also play important roles in breaking down methionine in the body. Vitamin B12 and folate supplements may be part of your treatment plan if the levels of these vitamins in your body are too low.
What about diet? Are changes required?

If you cannot lower your homocysteine levels enough with vitamin B6, then you will need to eat a special diet to help manage your condition.

A LOW-PROTEIN DIET

A low-protein diet limits the methionine you eat in order to keep your homocysteine levels under control. Specialist dietitians can suggest low-protein foods and menus that you like and that also fit into your lifestyle.

“At parties or during holidays I usually take at least one dish I know I can eat. My best friends all know I’ll bring my own food. Sometimes it’s still hard, though, when I’m with my family and they’ve ordered steak or prime rib. But then I tell myself that if I don’t do what I’m supposed to, I could end up with problems.”

— Pam P., person living with classical homocystinuria

Your low-protein diet plan may include three lists of foods:

• Foods you cannot eat because they will raise blood homocysteine levels. These foods may include meat, fish, eggs, and cheese. Foods such as beans, soy products, and nuts may also be on this list.

• Foods you can eat a little of. These “in between” foods contain some protein, but not as much as foods such as meat and eggs. Your dietitian will explain what these foods are and how much of them you can eat each day.

• Foods you can eat a lot more of, such as most fruits and vegetables which contain little or no protein. These foods are sometimes called “free” foods.

Staying on your special diet may be hard to do, especially when everyone else in your life is eating foods on your “cannot eat” list. A plan may look good on paper, but it won’t work if it stresses you out or you just can’t stick to it. Be honest with your dietitian and ask for help so that your diet plan is achievable and realistic.

“A methionine-free formula

If you have to eat a low-protein diet to lower and then maintain lower homocysteine levels, your body may not get enough of the essential amino acids it needs through the food that you eat. You can buy methionine-free formulas that contain the additional amino acids that your body needs. Taking formula will help prevent malnutrition that can occur if you don’t eat enough protein. However, some people may not like the taste of the formula. If you are one of these people, you can ask your specialist dietitian for creative formula mixtures that may work better for you.

The combination of diet and formula can help you maintain target blood homocysteine levels so you can lower your chances of developing symptoms or complications. The combination can also provide the nutrients you need to grow and be healthy.

“Samantha gets upset when I tell her she can’t have some of the foods her brother eats. Sometimes he wants to try her low-protein foods, but I tell him he can’t because it wouldn’t be fair to Samantha. He’s such a big help. He’s starting to read labels at grocery stores. He’ll say, “Mommy, this has 2 grams of protein per serving. Samantha can have this.”

— Amber G., mother of Samantha, who has classical homocystinuria
Aspirin or Warfarin

If you have had a blood clot or if you have a higher risk of developing a blood clot, your doctor may want you to take a medicine that can help prevent blood clots from developing. Aspirin and warfarin are two medicines used for this purpose.

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, cereals, and seafood, also contain tiny amounts of betaine.

Your doctor may add Cystadane® to your treatment plan to help lower your homocysteine blood levels. People with classical homocystinuria may have high blood levels of both homocysteine and methionine.

Cystadane® may worsen high methionine levels, possibly causing excess fluid to build up in the brain. So if you take Cystadane®, your doctor will regularly monitor your methionine blood levels to see if changes to your Cystadane® dosage or diet are needed.

The most common side effects of Cystadane® are nausea and gastrointestinal distress, based on a survey of doctors. For more information, visit www.cystadane.com.

“IT’S BEEN 6 YEARS SINCE I WAS PROPERLY DIAGNOSED WITH CLASSICAL HOMOCYSTINURIA, AND I FEEL LIKE I’VE GOTTEN A SECOND CHANCE AT LIFE. SINCE I STARTED EATING A LOW-PROTEIN DIET AND TAKING THE MEDICINES MY DOCTOR HAS PRESCRIBED, MY BLOOD HOMOCYSTEINE LEVELS HAVE BEEN WELL-CONTROLLED.”

— Pam P., person living with classical homocystinuria
There are many things you can do to meet the challenges of living with classical homocystinuria. 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 and methionine levels. Your blood test results will allow your doctor to see how well your treatment plan and diet are working and to adjust these plans as necessary. For adults, blood testing may be done every 6 months, or potentially more often if homocysteine levels are higher than desired. For children who need to eat a low-protein diet, blood testing may be done more frequently since they are still growing and their needs may change as they grow.

- Work with a specialist dietitian to plan and periodically update your low-protein diet plan when needed. Be sure your diet plan is manageable for you. If it’s not, keep working with your dietitian.

- See other doctors as needed. Your overall health and well-being are very important, and, as someone with classical homocystinuria, you’ll have added needs. Specifically, you should see doctors to monitor your vision, bone health, and heart health. These areas of your body are more likely to be affected by classical homocystinuria.

“\textit{When you first get the diagnosis, don’t panic and don’t go internet-crazy. Homocystinuria is manageable, even though it may not seem so at first.}”

- Amber G., mother of Samantha, who has classical homocystinuria

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**Losing control of blood homocysteine levels at any age may lead to serious health problems, such as learning problems and delays in child development, mental health problems, seizures, vision problems, and weak bones. Some complications, such as blood clots, may be potentially life-threatening.**

However, much evidence shows that controlling homocysteine levels can lower your chances of developing complications.

If you already have some complications, proper treatment may slow or stop their progression or prevent them from happening again.

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

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**What are some good ways to meet the challenges caused by classical homocystinuria?**
**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 help you achieve your target homocysteine levels. By following your plan, you can prevent or lessen further damage to areas of your body that are affected by high homocysteine levels.

- **Eat a low-protein diet without having to buy lots of expensive foods online.**
  Grocery stores may carry low-protein foods, such as some non-dairy cheeses and rice milk. Many grocery stores may also have a gluten-free section, and some packaged gluten-free foods may be lower in protein content compared to the non-gluten-free versions. Always read food labels, and check with your dietitian about any foods you aren’t sure about. Also, there are many low-protein recipes and other diet management tools online.

- **Eat as many “free” foods as you want.**
  Even if you must follow a low-protein diet. Many vegetables and fruits are “free” foods, so here’s to watermelon and green peppers!

- **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 classical homocystinuria. 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 tools may be useful if you need to follow a low-protein diet:**

- **AccuGo for HCU**
  – This app for iPhones, sponsored by HCU Network Australia, provides a quick and easy way to estimate and track protein and methionine in foods. The app uses data from Australia/New Zealand and USDA food lists, a community food list, and a personal food list.

- **HowMuchPhe.org**
  – This website provides access, by subscription, to a list of more than 7,000 low-protein foods. You can search for foods by name using any mobile device that connects to the internet. The site was originally developed for people with phenylketonuria (PKU), a rare genetic disease that also requires a low-protein diet.

- **CookForLove.org**
  – This website provides step-by-step instructions and cooking videos for making tasty and nutritious low-protein recipes. Most ingredients can be found in local grocery stores.
These organizations provide information about classical homocystinuria:

- HCU Network America – The mission of HCU Network America is to help people with homocystinuria (HCU) and related disorders manage their disease and 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.

- E-HOD – 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 clinical and diagnostic care protocols, and evaluating newborn screening programs.

"Be your own best advocate. Follow your instincts and do your own research if something doesn’t seem quite right. Join online support groups where others can help you find the right resources.” – Pam P., person living with classical homocystinuria.
concentrations. However, there has been no demonstrated correlation between Betaine concentrations and homocysteine levels.

Patients have taken CYSTADANE for many years without evidence of tolerance. There have been pediatric patients, including patients ranging in age from 24 days to 17 years (n=49) treated with CYSTADANE. The safety and effectiveness of CYSTADANE have been established in pediatric patients.

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. 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. 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)).

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:

\[
\text{CH}_3
\]

\[
\text{CH}_2 \quad \text{N}^+ \quad \text{CH}_3 \quad \text{COO}^- \quad \text{CH}_3
\]

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.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity and fertility studies have not been conducted with CYSTADANE. There is no evidence of genotoxicity 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 was 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 g/day, 3 patients received less than 6 g/day, 12 patients received doses from 6 to 15 g/day, and 5 patients received doses over 15 g/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). Homocysteine is formed nonenzymatically from two molecules of homocysteine, and both have been used to evaluate the effect of CYSTADANE in patients with homocystinuria. Plasma homocysteine or homocystine concentrations were reported numerically for 62 patients, and 61 of these patients showed decreases with CYSTADANE treatment. Homocysteine 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 folic acid. In most cases, adding CYSTADANE resulted in a further reduction of either homocysteine or homocystine concentrations.

16. HOW SUPPLIED/STORAGE AND HANDLING

CYSTADANE is available in plastic bottles containing 180 grams of betaine anhydrous as a white, granular, hygroscopic powder. Each bottle is equipped with a plastic child-resistant cap and is supplied with a polypropylene measuring scoop. One level scoop (1.7 mL) is equal to 1 gram of betaine anhydrous powder. NDC 52276-400-01 180 g/bottle.

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

17. PATIENT COUNSELING INFORMATION

Preparation and Administration Instructions
Instruct patients and caregivers to administer CYSTADANE as follows:
- Shake bottle lightly before removing cap.
- Measure the number of scoops for the patient’s dose with the scoop provided. One level scoop (1.7 mL) is equivalent to 1 gram of betaine anhydrous powder.
- Mix powder with 4 to 6 ounces (120 to 180 mL) of water, juice, milk, or formula until completely dissolved, or mix with food, then ingest mixture immediately.
- Always replace the cap tightly after using and protect bottle from moisture.

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CYSTADANE® betaine anhydrous for oral solution

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