This brochure will help you understand what MTHFR deficiency is, how it causes homocystinuria and 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 MTHFR deficiency? MTHFR stands for 5,10-methylenetetrahydrofolate reductase, which is an enzyme. Enzymes are proteins that help chemical reactions take place in the body.

This brochure focuses on severe MTHFR deficiency, which occurs when someone has MTHFR enzyme activity that is less than 20 percent of average. Severe MTHFR deficiency, which is rare, can cause serious symptoms. Less severe forms of MTHFR deficiency are quite common. These individuals generally do not develop symptoms because their MTHFR enzyme activity is only mildly or moderately reduced.

MTHFR deficiency is 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 MTHFR deficiency and how you can manage your condition.

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

*Pronounced METH-uh-leen-TEH-truh-high-DRO-foe-late

WHAT IS HOMOCYSTINURIA?

You may have heard the word “homocystinuria” for the first time when your doctor talked to you about possibly having MTHFR deficiency. Homocystinuria caused by MTHFR deficiency 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 homocysteine in your blood and urine. High levels of homocysteine can be harmful to your body.
Since too much homocysteine can harm your body, it needs to convert some of the homocysteine back to methionine. This process involves folate – also called vitamin B9 – that you get from the foods you eat. The MTHFR gene in your body produces the MTHFR enzyme, which activates a 2-step process to convert folate into 5-methyltetrahydrofolate or 5-MTHF. This is the form of folate that your body needs to convert homocysteine back to methionine.

When the process is working the way it should, your body uses 5-MTHF, along with other B vitamins and enzymes, to convert homocysteine back to methionine.

However, the process can break down if you have an abnormal variation of the MTHFR gene that makes:

- MTHFR enzyme that does not work properly, or
- Too little MTHFR enzyme or none at all

When this happens, your body cannot convert homocysteine back to methionine. This causes the level of homocysteine to build up and the level of methionine to decrease in your body. Both can lead to serious health problems.
MTHFR deficiency is a genetic disorder, which is another way of saying that the condition is inherited from your parents. It is a lifelong condition. MTHFR deficiency occurs when you inherit two copies of an abnormal variation of the MTHFR gene, one from each parent. The medical term for this kind of inheritance is autosomal recessive. The MTHFR gene helps convert the folate that you get from the foods you eat into 5-methyltetrahydrofolate (5-MTHF), the form of folate that your body needs.

If you have homocystinuria due to MTHFR deficiency 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 MTHFR 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 MTHFR deficiency may affect families. In this family, the parents, Darryl and Nia, are carriers of MTHFR deficiency. Each child in the family has a 1 in 4 chance of having MTHFR deficiency. In this case, Andre, their son, has MTHFR deficiency because he inherited two abnormal variations of the MTHFR gene. The other children – Jasmine, Austin, and Sofia – do not have MTHFR deficiency. But Jasmine and Austin are carriers of the deficiency because they have one normal copy and one abnormal variation of the MTHFR gene. Both of them could potentially pass on the affected gene to their future children. Sofia 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 MTHFR deficiency is much more common than having the condition. That’s why many people who are diagnosed with MTHFR deficiency have no known family history of homocystinuria.
How and when is MTHFR deficiency diagnosed?

**Newborn screening** for MTHFR deficiency is not done at this time. Therefore, the condition is diagnosed after symptoms begin to appear.

Symptoms may develop at different times for different people, so diagnosis can occur at any age. And because MTHFR deficiency is rare, some doctors may not recognize the non-specific symptoms right away and the diagnosis can be delayed.

**If you have homocystinuria due to MTHFR deficiency, you were born with the disorder, even if you didn’t have symptoms right away.**

Homocystinuria caused by MTHFR deficiency is diagnosed by lab tests that measure the blood levels of:

- Homocysteine – higher than normal
- Methionine – usually lower than normal
- Other molecules affected by folate metabolism that may be higher or lower than normal

Your doctor may want to confirm your diagnosis with additional testing, which may include:

- Biopsy of skin tissue to measure enzyme activity
- Molecular genetic testing to identify the abnormal MTHFR gene variation

How can MTHFR deficiency affect your health?

**MTHFR deficiency** can affect your health in many different ways. Most medical problems that occur are neurological, meaning they involve your brain, spinal cord, and nerves. Symptoms may affect your ability to develop, think, and move normally. Symptoms may also affect other parts of your body, such as your blood and eyes. Symptoms may vary, depending on what age they develop, and they can range from mild to severe.

**Early-onset MTHFR deficiency**

Most people with MTHFR deficiency develop signs and symptoms before they are a year old. This is the "early-onset" form of MTHFR deficiency. Early-onset symptoms are related to the lowest levels of MTHFR enzyme activity and tend to be more severe than symptoms that develop later.

**Common symptoms include:**

- Feeding problems, such as acting fussy or not wanting to nurse or take a bottle
- Failure to grow and gain weight as expected
- Seizures
- Drowsiness, lack of energy, reduced awareness
- Temporary stops in breathing (apnea)
- Floppy muscles and joints
- Buildup of fluid in the brain (hydrocephaly)
- Small head and brain size (microcephaly)
- Developmental delay, such as slow to sit up, walk, or talk
- Intellectual disability, such as learning difficulties or problems with memory or other thinking skills
- Eye disorders, such as eyes that do not point in the same direction (strabismus); rapid, rhythmic, jerky, or wobbling eye movements (nystagmus); or bleeding in the retina
How can MTHFR deficiency affect your health?

Late-onset MTHFR deficiency

Some people do not develop symptoms until after their first year of life and even into adulthood. This is the "late-onset" form of MTHFR deficiency. Late-onset symptoms may be milder than symptoms that develop in the first year of life. At first, individuals may have just one neurologic symptom before they eventually develop other symptoms.

Common symptoms include:
• Walking or gait disorders, mainly due to weakness in legs
• Other movement disorders resulting in spastic or jerky movements, caused by inability to coordinate muscle activity
• Epilepsy or seizures
• Decline in intellectual or cognitive abilities
• Behavior or mental health problems
• Blood clots in veins or arteries, including within the brain

Learning from your doctor that you have MTHFR deficiency may be unsettling for you and your family. But even though MTHFR deficiency is rare, there is information about how to treat it. Ideally you should be treated by a medical geneticist (metabolic specialist) who is familiar with managing MTHFR deficiency. A metabolic specialist is a doctor who specializes in treating genetic conditions that involve the body's metabolism.

Your healthcare team will develop a treatment plan based on your needs. You should work closely with the team to develop your plan.

How can MTHFR deficiency be managed?

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

Your treatment plan may include:
- Taking certain medicines to lower homocysteine
- Taking other therapies

A low-protein diet is often needed for people who have a different type of homocystinuria called classical homocystinuria. However, a low-protein diet is not recommended for people with MTHFR deficiency. This is because a low-protein diet also reduces methionine, which can be lower than normal if you have MTHFR deficiency, and low methionine levels can be harmful to the body.
**What medicines or other therapies may be helpful for MTHFR deficiency?**

**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.

The most common side effects of CYSTADANE are nausea and gastrointestinal distress, based on a survey of doctors.

**Other therapies**

Your doctor may add other therapies to your treatment plan, such as:

- Folic acid or 5-MTHF (a form of folate)
- Other B vitamins including vitamin B6, cobalamin, or riboflavin
- Carnitine (a chemical made from two amino acids)
- Methionine

**CYSTADANE® (betaine anhydrous for oral solution) is indicated in adults and children 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.
**Why is it important to follow your treatment plan?**

**Losing control** of blood homocysteine and methionine levels at any age may lead to serious health problems. However, with the right treatment, some existing symptoms may not get worse or they may become less severe or less frequent. Some potential symptoms or complications may even be prevented. Proper treatment may have a positive effect on:

- Feeding ability
- Psychomotor development (psychomotor skills involve the brain and muscles, such as turning over, sitting, crawling, walking, talking, and solving problems)
- Other symptoms or disabilities related to the brain
- Survival

Early diagnosis and lifelong treatment help prevent complications and result in the best outcomes.

**What are some good ways to meet the challenges caused by MTHFR deficiency?**

There are many things you can do to meet the challenges of living with MTHFR deficiency. 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 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 MTHFR deficiency, you may have other health issues. Doctors will be on the lookout for problems that can result from your disorder.

**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 and methionine 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 disorder.

- **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 MTHFR deficiency. If they are pregnant, have them alert their doctors. 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 MTHFR deficiency:

- **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.

- **E-HOD** – European Network and Registry for Homocystinurias and Methylthionine Defects – The aim of E-HOD is to improve the health of people affected with homocystinuria and methylation defects by developing a patient registry, developing diagnostic and clinical care protocols, and evaluating newborn screening programs.

**CONTRAINDICATIONS**

None (4)

**WARNINGS AND PRECAUTIONS**

- Hypomethioninemia in Patients with CBS Deficiency: CYSTADANE may worsen elevated plasma methionine concentrations and central 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 1-888-575-8544, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

**PUBLICATION**

Revised 10/2019
Table 1: Number of Patients with Adverse Reactions to CYSTADANE by Physician Survey

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Number of Patients</th>
</tr>
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<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal distress</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>“Bad Taste”</td>
<td>1</td>
</tr>
<tr>
<td>“Caused Odor”</td>
<td>1</td>
</tr>
<tr>
<td>Questionable psychological changes</td>
<td>1</td>
</tr>
<tr>
<td>“Aspirated the powder”</td>
<td>1</td>
</tr>
</tbody>
</table>

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 toxicity 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 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:

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

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.

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 pretreatment 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 folic acid (folate), vitamin B12 (cobalamin), and choline, and folic acid 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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