RECORDATI RARE DISEASES INC.
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Dear Healthcare Provider,

The appeals process with most insurance plans often requires the submission of a Letter of Appeal. The purpose of this exemplar letter is to assist your office in developing a customized Letter of Appeal, which addresses the reasons CYSTADANE (betaine anhydrous for oral solution) was denied, as well as outline the medical justification for CYSTADANE therapy.

Please note - this letter exemplar should only be used as a guide for patients with CBS deficiency treated with CYSTADANE. However, it is suggested that your Letter of Appeal include:

1. The reason(s) CYSTADANE therapy was denied,
2. Response or rebuttal to each reason CYSTADANE was denied, and
3. Supporting documentation (such as lab results) justifying the need for CYSTADANE if needed.

As you know, each patient will have their own unique and specific reasons for needing CYSTADANE therapy. In addition, each insurance plan may have their own rules and guidelines for approving CYSTADANE.

This sample letter and related information are provided for informational purposes only. It is the responsibility of the HCP and/or their office staff, as appropriate, to determine the correct diagnosis, treatment protocol, and content of all such letters and related forms for each individual patient. Recordati Rare Diseases (RRD) does not guarantee coverage or reimbursement for the product. There is no requirement that any patient or healthcare provider use any RRD product in exchange for this information, and this template is not meant to substitute for a prescriber's independent medical decision-making.

For full Prescribing Information and Instructions for Use, please go to www.CYSTADANE.com.

Sincerely,
The CYSTADANE Team
Phone: (888)-487-4703
Fax: (855)-813-2039

ON OFFICE LETTERHEAD INLCUDING PROVIDER NAME AND ADDRESS

Name

Address

Phone

Fax

CYSTADANE® (betaine anhydrous for oral solution)

Letter of Appeal

EXEMPLAR

(Date)

(Payer Name)

(Payer Address)

Patient Name: (Patient Name)

Patient Date of Birth: (Patient DOB)

Policy Number: (Policy Number)

Group Number: (Group Number)

Case Number: (Case Number)

Subject: Letter of Appeal regarding CYSTADANE® (betaine anhydrous for oral solution)

To Whom It May Concern:

I am writing to request an APPEAL of the decision to deny CYSTADANE for my patient (**Patient name**). (**Patient name**) has been diagnosed with homocystinuria caused by CBS deficiency and requires treatment with CYSTADANE.

CYSTADANE (betaine anhydrous for oral solution) 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:

- Cystathionine beta-synthase (CBS) deficiency
- 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
- Cobalamin cofactor metabolism (cbl) defect

This patient has been receiving treatment with CYSTADANE since (**Treatment initiation date**) and had seen the following clinical outcomes: (**list outcomes**).

Our office received a denial for CYSTADANE on (**date**). In that denial, CYSTADANE was denied due to the following reasons:

1.
2.
3.

I disagree with this decision. In my clinical judgement, treatment with CYSTADANE is medically necessary due to the following reasons:

1.
2.
3.

Treatment Plan:
Classical homocystinuria is a rare inherited disorder that impairs the body's ability to metabolize, or break down, an amino acid homocysteine. High blood homocysteine levels can cause nearsightedness (myopia), dislocation of the lens at the front of the eye, an increased risk of abnormal blood clotting, and brittle bones that are prone to fracture (osteoporosis) or other skeletal abnormalities. Some affected individuals also have developmental delay and learning problems.

Lowering the homocysteine levels is the primary objective in the treatment of patients with classical homocystinuria.

My intended use of CYSTADANE will be to continue treatment at the recommended dosage: 6 grams per day, administered orally in divided doses of 3 grams twice daily.

Please note that according to the CYSTADANE Prescribing Information, 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 71to 83%, regardless of the pretreatment 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

I would appreciate your reconsideration of this denial and ask that you reverse your decision and approve CYSTADANE for (**patient name**).

If you have any questions or wish to conduct a Peer to Peer discussion, feel free to contact me at (**enter phone number**).

Thank you for your time and consideration!
(**First and Last name, MD**)