Betaine anhydrous (Cystadane®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO113

Description

Betaine anhydrous (Cystadane) is an orally administered endogenous metabolite of choline.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
betaine anhydrous (Cystadane)	1 g/1.7 mL powder	Homocystinuria	540 grams/30 days

Initial Evaluation

I. Betaine anhydrous (Cystadane) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a metabolic or genetic disease specialist; **AND**
   B. A diagnosis of **homocystinuria** when the following are met:
      1. Diagnosis associated with one of the following (i, ii, or iii):
         i. Cystathionine beta-synthase (CBS) deficiency; **AND**
            a. Treatment with **ALL** of the following has been ineffective, contraindicated, or not tolerated:
               i. Vitamin B6 (pyridoxine)
               ii. Vitamin B12 (cyanocobalamin)
               iii. Folic Acid
               iv. Diet restrictions; **OR**
         ii. Homocystinuria associated 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency; **OR**
         iii. Cobalamin cofactor metabolism (cbl) defect

II. Betaine anhydrous (Cystadane) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-alcoholic fatty liver

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Betaine anhydrous (Cystadane) is indicated in pediatric and adult patients for the treatment of homocystinuria, and is used to decrease elevated homocysteine blood concentrations. Homocystinuria results from deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylenetetrahydrofolate reductase (MTHFR), and/or cobalamin cofactor metabolism (CBL).
II. Homocystinuria is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. It may result from a deficiency of several enzymes involved in the conversion of methionine to cysteine or, less commonly, it is due to impaired conversion of the compound homocysteine to methionine. There are multiple forms of homocystinuria, which are distinguished by their signs, symptoms, and genetic cause. Clinical manifestations of homocystinuria includes developmental delay, Marfanoid appearance, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. The signs and symptoms of homocystinuria usually develop within the first year of life; although, the mildly-affected may not develop features until later in childhood or adulthood.
III. Guidelines for CBS deficiency state:
    - Betaine should be considered as adjunct treatment in patients who cannot achieve target levels of homocysteine by other means. Betaine treatment alone seldom achieves target homocysteine levels in those with a pyridoxine-unresponsive CBS deficiency. It is best used as adjunct treatment in patients who are partially responsive to pyridoxine, or, who are on dietary treatment but cannot achieve adequate control.
    - Patient response to betaine can vary, and, optimal doses require individualization. Standard initial dosing for children is 50 mg/kg twice daily; meanwhile, adults start at three grams two times a day. The dose and frequency are adjusted to the response of treatment with an added note that exceeding a dose of 150-200 mg/kg/day is unlikely to result in any additional benefit.
IV. Guidelines for MTHFR deficiency state:
    - Early identification and treatment with betaine for MTHFR deficiency is strongly recommended. Pre-symptomatic betaine treatment prevents severe neurological impairment with a high quality of evidence.

Investigational or Not Medically Necessary Uses

I. With limited evidence available, betaine anhydrous (Cystadane) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Non-alcoholic fatty liver (NAFLD)
      i. Treatment betaine anhydrous (Cystadane) is not listed within the American Association for the Study of Liver Diseases (AASLD) NAFLD guidelines.

References

1. Cystadane [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. October 2018.
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4. National Organization for Rare Disorders. Homocystinuria due to Cystathionine Beta-Synthase Deficiency. Available at: https://rarediseases.org/rare-diseases/homocystinuria-due-to-cystathionine-beta-synthase-deficiency/.
5. UpToDate, Inc. Overview of homocysteine. UpToDate [database online]. Waltham, MA. Last updated November 13, 2019 Available at: http://www.uptodate.com/home/index.html.
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7. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, and MTHFR deficiency. J Inherit Metab Dis 2017; 40:21-48.
8. Miglio F, Rovati LC, Santoro A, et al: Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis. Arzneimmittelforschung Drug Res 2000; 50(8):722-727.
9. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357.

Policy Implementation/Update:

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Action and Summary of Changes	**Date**