09-J1000-26

Original Effective Date: 07/15/10

Reviewed: 05/08/13

Revised: 01/01/20

Subject: Betaine, anhydrous (Cystadane®) Oral Solution

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Accumulation of homocysteine and homocystinuria occur as a result of inborn errors of cystathionine beta-synthase (CBS), 5,10-methylenetetrahydrofolate reductase (MTHFR), or cobalamin cofactor (cbl) synthesis. Elevated blood homocysteine concentrations are associated with clinical complications including thrombosis, osteoporosis, skeletal abnormalities, ectopia lentis (ocular lens dislocation), weakness, incoordination, peripheral neuropathies/paresthesias, memory impairment, and a high frequency of mental retardation. In the case of MTHFR deficiency, defective methionine turnover is thought to result in demyelination in the brain and subacute combined degeneration of the spinal cord. In pediatric subjects, the most severe form of the disease can be manifested within the first months or years of life by lethargy, failure to thrive, developmental delays, seizures, or lenticular displacement. In some cases of cystathionine beta-synthase deficiency, treatment with pyridoxine 50 to 1000 mg/day ameliorates the biochemical abnormality; the primary treatment of individuals unresponsive to pyridoxine has been a diet low in methionine and supplemented with cystine. Individuals unable to adapt to such a diet are often treated with antiplatelet agents to reduce the risk of thromboembolic complications.

Betaine, anhydrous (Cystadane®) also known as trimethylglycine is a methyl group donor which is effective for the treatment of homocystinuria. It occurs naturally in the human body, is the major metabolite of choline and is present in small amounts in foods such as beets, spinach, cereals, and seafood. In therapeutic doses, betaine facilitates the remethylation of homocysteine to methionine. In its conversion to dimethylglycine, betaine donates methyl groups to homocysteine to form methionine, catalyzed by betaine-homocysteine methyltransferase. As a result, toxic blood levels of homocysteine are reduced in these subjects, usually to 20 to 30% or less of pretreatment levels. Individuals have been treated successfully without adverse effects within the first months or years of life with betaine in doses of 6 grams or more per day with resultant biochemical and clinical improvement.

Plasma concentrations of homocysteine are decreased in nearly all subjects treated with betaine. In some studies, clinical improvement was reported in approximately 75% of subjects receiving betaine. Many subjects were also receiving other therapies such as pyridoxine, cobalamin, and folic acid with variable responses. In most cases, adding betaine to the regimen resulted in a further reduction in plasma homocysteine. Betaine lowered plasma homocysteine levels in 3 types of homocystinuria (i.e., cystathionine beta-synthase (CBS) deficiency, 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency, and cobalamin cofactor (cbl) defect).

Betaine has also been demonstrated to increase low plasma methionine and S-adenosylmethionine (SAM) levels in subjects with MTHFR deficiency and cbl defect. In CBS-deficient individuals, large increases in methionine levels have been observed; however, this increase does not appear to be associated with adverse clinical consequences.[1]

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of betaine, anhydrous (Cystadane®) **meets the definition of medical necessity** for members meeting **ALL** of the following:

1. Member is diagnosed with homocystinuria
2. Member has failed all of the following:
    a. Vitamin B6 (pyridoxine)
    b. Vitamin B12 (cyanocobalamin)
    c. Folic Acid
    d. Diet restrictions

Approval duration: 1 year

Continuation of betaine, anhydrous (Cystadane®) **meets the definition of medical necessity** for members meeting the following:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of homocystinuria or other FDA-approved diagnosis, **OR** the member has previously met all indication-specific initiation criteria

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Homocystinuria

Adult: Usual dosing is 6 g/day administered orally in divided doses of 3 g twice daily. Dosage can be gradually increased until plasma homocysteine is undetectable or present only in small amounts. Dosages of up to 20 g/day have been necessary to control homocysteine levels in some members.

Children 3 years of age and older: usual dosing is 6 g/day administered orally in divided doses of 3 g twice daily. Dosage can be gradually increased until plasma homocysteine is undetectable or present only in small amounts. Dosages of up to 20 g/day have been necessary to control homocysteine levels in some members.

Children younger than 3 years of age: the initial dosage is 100 mg/kg/day. Dosage can be titrated by increasing weekly 100 mg/kg increments. Dosages of up to 20 g/day have been necessary to control homocysteine levels in some members.

Preparation for administration: Measure prescribed amount with the measuring scoop provided (one level 1.7 mL scoop is equal to 1 g of betaine anhydrous powder) and then dissolve in 120 to 180 mL (4 to 6 oz) of water for immediate ingestion.

PRECAUTIONS:

Hypermethioninemia

Members with Homocystinuria due to cystathionine beta-synthase (CBS) deficiency may also have elevated plasma methionine concentrations. Treatment with betaine, anhydrous may further increase methionine concentrations due to the remethylation of homocysteine to methionine. Cerebral edema has been reported in members with hypermethioninemia, including a few members treated with betaine, anhydrous. Plasma methionine concentrations should be monitored in members with CBS deficiency. Plasma methionine concentrations should be kept below 1,000 µmol/L through dietary modification and, if necessary, a reduction of betaine, anhydrous dose.

BILLING/CODING INFORMATION:

Oral agents are generally administered through the pharmacy benefit.

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic,

ICD-10 Diagnosis Codes That Support Medical Necessity

E72.11	Homocystinuria

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Homocystinuria: also known as cystathionine beta synthase deficiency or CBS deficiency is an inherited disorder of the metabolism of the amino acid methionine, often involving cystathionine beta synthase. It is an inherited autosomal recessive trait, which means a child needs to inherit the defective gene from both parents to be affected.

Hypermethioninemia: an excess of the amino acid methionine, in the blood. This condition can occur when methionine is not broken down properly in the body.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

REFERENCES:

1. Azzabi S, Barhoumi A, Omar S, Ben Hassine L, Cherif E, Kooki C, Mrad R, Chaabouni H, Kaabachi N, Khalfallah N. Late revelation of homocysteinuria: clinical, biological and progressive aspects. Pathol Bio (Paris). 2009 Jul; 57(5):451-5.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2019 [cited 11/1/19]. Available from: http://www.clinicalpharmacology.com/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 11/1/19]. Available from: http://www.thomsonhc.com/.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 11/1/19]. Available from: http://clinicaltrials.gov/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

07/15/10	New Medical Coverage Guideline.
06/15/11	Review and revision to guideline; consisting of updating references.
06/15/12	Review and revision to guideline; consisting of updating coding and references.

06/15/13	No Longer Review
11/01/15	Revision: ICD-9 Codes deleted.
01/01/20	Revision to guidelines; addition of continuation criteria to position statement