Effective Date **1/1/2024**
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Coverage Policy Number **IP0465**

Betaine for Individual and Family Plans

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for betaine anhydrous for oral solution (Cystadane®) for Individual and Family Plans.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Betaine (Cystadane®) is considered medically necessary when the following are met:

1. **Homocystinuria.** Individual meets the **ALL** of the following criteria (A, B and C):
   A. Documented diagnosis of **ONE** of the following (i, ii, or iii) is confirmed by enzymatic, biochemical, or genetic analysis:
      i. Cystathionine beta-synthase (CBS) deficiency
      ii. 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
      iii. Cobalamin cofactor metabolism (cbl) defect

B. Prescribed by or in consultation with a clinical geneticist or metabolic disease specialist
C. Non-Covered Product Criteria is met, refer to below table

Individual and Family Plan Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Cystadane (betaine)	Documentation of the following: 1. Trial of **betaine trimethylglycine powder for solution** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Betaine (Cystadane) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, decrease in cysteine levels).

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

Background

OVERVIEW
Betaine anhydrous powder (Cystadane, generic), a methylating agent, is indicated for the treatment of homocystinuria to decrease elevated homocysteine blood concentrations in pediatric and adult patients.[1] Included within the category of homocystinuria are cystathionine beta-synthase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and cobalamin cofactor metabolism defect.

Disease Overview
Homocystinuria is a group of rare, autosomal recessive disorders caused by mutations in specific enzymes that metabolize amino acids.[2,3] Elevated levels of homocysteine can lead to abnormalities in the central nervous system, eye, skeletal system, and vascular system.

Clinical Efficacy
Clinical and observational studies demonstrated patients with homocystinuria who received betaine anhydrous powder had significant reductions plasma homocystine or homocysteine concentrations.[1] Additionally, improvement in seizures, or behavioral and cognitive functioning were reported for many patients. Many of these patients were also taking other therapies such as vitamin B6 (pyridoxine), vitamin B12 (cobalamin), and folate with variable biochemical responses.

DIAGNOSTIC INFORMATION:

Cystathionine beta-synthase (CBS) deficiency:
- Gene: *CBS*

- Enzyme: cystathionine β-synthase
- Inheritance: autosomal recessive
- Biochemical findings:
    - Plasma amino acids: elevated methionine
    - Homocysteine: elevated

5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency

- Gene: *MTHFR*
- Enzyme: Methylenetetrahydrofolate reductase
- Inheritance: autosomal recessive
- Biochemical findings:
    - Plasma amino acids: low/normal methionine
    - Homocysteine: elevated

Cobalamin cofactor metabolism (cbl) defect

- Genes: *MMACHC* or *PRDX1* (*cblC*), *MMADHC* (*cblD*-combined and *cblD*-homocystinuria), *MTRR* (*cblE*), *LMBRD1* (*cblF*), *MTR* (*cblG*), *ABCD4* (*cblJ*), *THAP11*(*cblX*-like), *ZNF143*(*cblX*-like), or *HCFC1* (*cblX*)
- Inheritance: autosomal recessive, except cblX (X-linked)
- Biochemical findings:
    - Plasma amino acids: low/normal methionine
    - Homocysteine: elevated
    - Methylmalonic acid: elevated
    - Acylcarnitine profile: elevated propionylcarnitine (C3)

References

1. Cystadane® powder [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; November 2018.
2. Truitt C, Hoff WD, Deole R. Health functionalities of betaine in patients with homocystinuria. *Front Nutr*. 2021 Sep 9;8:690359.
3. Morris A, Kožich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017 Jan;40(1):49-74.