Effective Date.....**12/15/2024**
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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. 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.

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, C and D):
    A. Documented diagnosis based on genetic testing demonstrating **ONE** of the following (i, ii, or iii)
        i. Cystathionine beta-synthase (CBS) deficiency
        ii. 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency
        iii. Cobalamin cofactor metabolism (cbl) defect
    B. Individual has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation

C. The medication is prescribed by, or in consultation with, a clinical geneticist, metabolic disease specialist, or a physician who specializes in the management of homocystinuria
D. Preferred product criteria is met for the product as listed in the below table

Individual and Family Plans:

Product	Criteria
Cystadane (betaine)	The individual has tried the bioequivalent generic product, **betaine anhydrous powder for solution,** AND cannot take due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which would result, per the prescriber, 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.

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

Reauthorization Criteria

Continuation of Betaine (Cystadane) is considered medically necessary for Homocystinuria when the above medical necessity 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 (criteria will be updated as new published data are available).

Background

OVERVIEW
Betaine anhydrous powder (Cystadane, generic), a methylating agent, is indicated for the treatment of **homocystinuria** to decrease elevated homocysteine blood concentrations in adults and pediatric 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.

References

1. Cystadane® powder [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; October 2019.
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.

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Homocystinuria** **Updated** criterion **from "**Documented diagnosis of **ONE** of the following (i, ii, or iii) is confirmed by enzymatic, biochemical, or genetic analysis" **to** "Documented diagnosis based on genetic testing demonstrating **ONE** of the following (i, ii, or iii)." **Added** criterion "Patient has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation." **Updated** criterion **from** "The medication is prescribed by or in consultation with a clinical geneticist or metabolic disease specialist" **to** "The medication is prescribed by or in consultation with a clinical geneticist, metabolic disease specialist, or a physician who specializes in the management of homocystinuria."	12/15/2024

The policy effective date is in force until updated or retired.