



## Drug Coverage Policy

Effective Date .....12/01/2025  
Coverage Policy Number.....IP0465  
Policy Title.....Cystadane

# Metabolic Disorders – Betaine Anhydrous for Individual and Family Plans

- Cystadane® (betaine anhydrous powder – Recordati Rare Diseases, generic)

### **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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see “Coding Information” below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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.

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## 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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>1</sup> 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.

## Coverage Policy

### POLICY STATEMENT

Prior Authorization is required for benefit coverage of betaine anhydrous powder (Cystadane, generic). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with betaine anhydrous powder (Cystadane, generic) as well as the monitoring required for adverse events and long-term efficacy, approval requires betaine anhydrous powder (Cystadane, generic) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Documentation:** Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

**Betaine anhydrous powder (Cystadane, generic) is considered medically necessary when the following are met:**

### FDA-Approved Indication

1. **Homocystinuria.** Approve for 1 year if the patient meets ALL of the following (A, B, C and D):
  - A) Patient has a confirmed diagnosis based on genetic testing demonstrating ONE of the following (i, ii, or iii) **[documentation required]**:
    - i. Cystathionine beta-synthase deficiency; OR
    - ii. 5,10-methylenetetrahydrofolate reductase deficiency; OR
    - iii. Cobalamin cofactor metabolism defect; AND

- B)** Patient has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation; AND
- C)** The medication is prescribed by or in consultation with a 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
<b>Cystadane</b> (betaine)	NOTE: A multisource Brand product is being requested. The patient should use the preferred bioequivalent generic product. Criteria: Approve if the Brand product is being requested 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, per the prescriber, would result in a significant allergy or serious adverse reaction [ <b>documentation required</b> ].

**Conditions Not Covered**

**Betaine anhydrous powder (Cystadane, generic) for any other use is considered not medically necessary. Criteria will be updated as new published data are available.**

**References**

1. Cystadane® powder [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; November 2024.
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	<b>Homocystinuria</b> <b>Updated</b> criterion from “Documented diagnosis of <b>ONE</b> of the following (i, ii, or iii) is confirmed by enzymatic, biochemical, or genetic analysis” to “Documented diagnosis based on genetic testing demonstrating <b>ONE</b> of the following (i, ii, or iii).” <b>Added</b> criterion “Patient has tried or is concurrently receiving vitamin B6 (pyridoxine), vitamin B12 (cobalamin), or folate supplementation.” <b>Updated</b> 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
Annual Revision	<b>Updated</b> policy title from “Betaine for Individual and Family Plans” to “Metabolic Disorders – Betaine Anhydrous for Individual and Family Plans.”	12/1/2025

	<b>Added</b> [documentation required] to indication and to the preferred product table.	
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The policy effective date is in force until updated or retired.

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