Drug Coverage Policy

Effective Date.....04/01/2026
Coverage Policy Number.....IP0786
Policy Title.....Forzinity

Barth Syndrome – Forzinity for Individual and Family Plans

- Forzinity® (elamipretide subcutaneous injection)

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.

Overview
Forzinity, a mitochondrial protective agent, is indicated to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg.[1]

Forzinity was approved under accelerated approval based on an improvement in knee extensor muscle strength, an intermediate clinical endpoint.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Disease Overview
Barth syndrome is an ultra-rare, life-threatening, X-linked, infantile-onset, mitochondrial disorder characterized by cardiomyopathy, hypotonia, growth delay, neutropenia, and infections.[2] Currently, less than 250 patients have been diagnosed globally, but it is estimated that the disorder may be substantially underdiagnosed due to the variable clinical manifestation.[3] Barth syndrome is caused by mutations in the *TAZ* gene.[4] The *TAZ* gene is responsible for encoding the protein tafazzin. This protein is essential for the production of mature cardiolipin (CL), a mitochondrial-specific phospholipid. CL helps to maintain mitochondrial structure, energy production, and overall cellular function. Mutations in the TAZ gene lead to an abnormal CL composition. There is an accumulation of monolysocardiolipin ([MLCL] a precursor) and a deficiency of mature CL. Abnormal CL affects the structure and function of the inner mitochondrial membrane. Generally, tissues with the highest energy demands (e.g., heart and skeletal muscle) are most affected, leading to clinical features such as cardiomyopathy and muscle weakness. Additionally, mitochondrial dysfunction affects neutrophil activity, contributing to increased infection risk. The phenotype of Barth syndrome is variable but most frequently manifests as infantile-onset cardiomyopathy, myopathy, and neutropenia.[5] Additional features may include exercise intolerance, lactic acidosis, low serum and muscle carnitine, and increased organic acids in the serum or urine. A presumed diagnosis may be confirmed by molecular genetic analysis or by biochemical laboratory findings.[6] Biochemical findings include increased MLCL, decreased remodeled CL, and an abnormal MLCL/CL ratio in bloodspots, cells, and tissues.[7,8] Increased 3-methylglutaconic acid, 3-methylglutaric acid, and 2-ethylhydracrylic acid on urine organic acids analysis is also often seen.

Clinical Efficacy
In the pivotal study, patients were $\geq$ 12 years of age and weighed $\geq$ 30 kg with genetically confirmed disease.[9,10] Efficacy endpoints evaluated were the change from baseline in the six-minute walk test (6MWT), the total fatigue score (TFS), knee extensor muscle strength, 5 times sit-to-stand test (5xSST), and the SWAY balance score. During the randomized, double-blind component of the study (Part 1), a significant difference between Forzinity and placebo was not observed for any of the endpoints evaluated. In the open-label component of the pivotal study (Part 2), a significant improvement from baseline was observed through Week 168 in the 6MWT, muscle strength, and 5xSST; the mean TFS trended toward improvement from baseline at all measured timepoints through Week 168. Additionally, the effect of Forzinity on echocardiographic parameters or CL findings was evaluated to establish confirmatory evidence of clinical benefit. Of note, the reported 2D and 3D echocardiographic parameters at baseline were within the normal range in all patients. At the end of Part 1, there was no difference between Forzinity and placebo in any of the echocardiographic parameters. Furthermore, subsequent changes reported in Part 2 were small, and generally still within the refence range of normal.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Forzinity. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of

patients treated with Forzinity as well as the monitoring required for adverse events and long-term efficacy, approval requires Forzinity 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. All documentation must include patient-specific identifying information.

Forzinity is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Barth Syndrome.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** The patient weighs ≥ 30 kg; AND
     - **ii.** The diagnosis is established by ONE of the following (a, b, or c):
       - **a)** Patient has a laboratory test demonstrating an increased ratio of monolysocardiolipin (MLCL)/cardiolipin (CL) on erythrocytes, tissue, fibroblasts, or stored neonatal bloodspots **[documentation required]**; OR
       - **b)** Patient has a laboratory test demonstrating elevated 3-methylglutaric acid, 3-methylglutaconic acid (3-MGC), and 2-ethylhydracrylic acid on urine organic acids analysis **[documentation required]**; OR
       - **c)** Patient has a molecular genetic test demonstrating a hemizygous pathogenic variant in the tafazzin (*TAZ*) gene **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with a geneticist, cardiologist, metabolic specialist, hematologist, pediatrician, or a physician who specializes in the treatment of mitochondrial disorders; OR
   - **B)** Patient is Currently Receiving Forzinity. Approve if the patients meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 1 year; AND
       Note: A patient who has received < 1 year of therapy or who is restarting therapy with the requested drug should be considered under criterion A (Initial Therapy).
     - **ii.** According to the prescriber, the patient has demonstrated a clinical response, defined as stabilization or lack of decline from baseline (prior to initiating Forzinity).
       Note: Examples of a clinical response include stabilization or lack of decline in muscle strength, balance, six-minute walking distance, or fatigue.

Conditions Not Covered

Forzinity for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

References

1. Forzinity™ subcutaneous injection [prescribing information]. Needham, MA: Stealth; September 2025.

2. Barth syndrome. National organization for rare disorders NORD. Updated July 30, 2019. Available at: https://rarediseases.org/rare-diseases/barth-syndrome/. Accessed on January 07, 2025.
3. Taylor C, Rao ES, Pierre G, et al. Clinical presentation and natural history of Barth Syndrome: An overview. *J Inherit Metab Dis.* 2022 Jan;45(1):7-16.
4. Thompson R, Jefferies J, Wang S, et al. Current and future treatment approaches for Barth syndrome. *J Inherit Metab Dis*. 2022 Jan;45(1):17-28.
5. Finsterer J. Barth syndrome: mechanisms and management. *Appl Clin Genet*. 2019 Jun 5;12:95-106.
6. Barth syndrome. Barth Syndrome Foundation. Updated March 3, 2019. Available at: https://www.barthsyndrome.org/barthsyndrome/. Accessed on October 13, 2025.
7. Hornby B, Thompson WR, Almuqbil M, et al. Natural history comparison study to assess the efficacy of elamipretide in patients with Barth syndrome. *Orphanet J Rare Dis*. 2022 Sep 2;17(1):336 [Epub].
8. Ferreira C, Pierre G, Thompson R, et al. Barth Syndrome. 2014 Oct 9 [Updated 2020 Jul 9]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK247162/. Access on October 13, 2025.
9. Thompson WR, Hornby B, Manuel R, et al. A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism. *Genet Med.* 2021;23(3):471-478.
10. Thompson WR, Manuel R, Abbruscato A, et al. Long-term efficacy and safety of elamipretide in patients with Barth syndrome: 168-week open-label extension results of TAZPOWER. *Genet Med.* 2024;26(7):101138.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy.	04/01/2026

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