elamipretide (Forzinity ™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO333

Description

Elamipretide (Forzinity) is a subcutaneously administered mitochondrial protective agent.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
elamipretide (Forzinity)	Barth Syndrome	280 mg/3.5 mL (80 mg/mL) vials	14 mL/ 28 days

Initial Evaluation

I. **Elamipretide (Forzinity)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a cardiologist and/or metabolic medicine specialist who practices at, or consults with, a Center of Excellence for Barth Syndrome; **AND**
   B. Documentation member weighs 30 kg or more; **AND**
   C. A diagnosis of **Barth Syndrome** when the following are met:
      1. Documentation of a TAFAZZIN mutation; **AND**
      2. Documentation of a baseline assessment [e.g., MLCL/CL_4 ratio, 6-minute walk test (6MWT), knee-extensor strength, etc.] within the past 3 months; **AND**
      3. Attestation member has been optimized on supportive therapies (e.g., medications for the management of heart failure, physical therapy, medications for the prevention and treatment of infections, etc.); **AND**
      4. Provider attestation that member is not a candidate for clinical trial participation

II. Elamipretide (Forzinity) is considered investigational when used for all other conditions, including but not limited to:
   A. Dry age-related macular degeneration (AMD)
   B. Primary mitochondrial myopathy (PMM)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Documentation member has exhibited improvement of disease symptoms from an objective baseline assessment [e.g., improvement in 6MWT, fatigue, stability of cardiac function, normalization of MLCL/CL_4 ratio, knee-extensor strength, etc.]

Supporting Evidence

I. Barth Syndrome (BTHS) is a rare X-linked, inborn error of the metabolism caused by mutations in the *TAFAZZIN* gene. *TAFAZZIN* encodes a mitochondrial phospholipid transacylase (tafazzin). Defective tafazzin activity leads to low CL_4, the main cardiolipin (CL) phospholipid in the inner mitochondrial membrane in heart and skeletal muscle. When CL_4 production does not correctly occur, it results in an increase in the CL_4 precursor, MLCL, and therefore, an increased MLCL/CL_4 ratio. The disrupted ratio alters the function of the inner mitochondrial membrane, compromising the electron transport chain and aerobic respiration.

II. Barth Syndrome (BTHS) is an ultra-rare disease with only 230 to 250 affected patients worldwide. The disease is characterized by exercise intolerance, muscle weakness, debilitating fatigue, cardiomyopathy, heart failure, skeletal myopathy, neutropenia, delayed growth, and reduced life expectancy. Due to the complexity of care, consultation with a physician specializing in the treatment of Barth Syndrome is required.

III. Cardiomyopathy is the leading cause of death in patients with BTHS, which is described as having an undulating course, whereby left ventricular (LV) tissue can remodel. Infancy and early childhood are particularly high-risk periods for cardiac transplant and death, with 85% of early deaths occurring by age five, those who survive experience improvements and stabilization of their cardiac function in the middle childhood years. As patients with BTHS age, their LV size may remain above the upper limit of normal. LV function may be low normal or mildly depressed whereas others experience deterioration in cardiac function, necessitating heart transplantation. The predominant disease manifestations in adolescents and adults are fatigue, poor stamina, and exercise intolerance. The quality of life and daily functioning of patients are significantly affected throughout their lives.

IV. Elamipretide (Forzinity) was studied in a Phase 2/3, randomized, double-blind, placebo-controlled crossover trial (TAZPOWER) (N=12) which subsequently continued into an open-label extension study (TAZPOWER OLE) (N=8). Participants were studied at a single site and randomized to elamipretide (Forzinity) or placebo for treatment period which continued for twelve weeks. Patients were then discontinued from therapies for four weeks (washout) and crossed over to the other treatment for another duration of twelve weeks. The open label extension allowed all patients to restart elamipretide (Forzinity) for 168 weeks.

V. The average age at enrollment was 19.5 years (range 12–35 years) and all enrollees were male. At baseline, two of twelve individuals had neutropenia as defined by an absolute neutrophil count <1500 cells/µL, and six individuals received granulocyte colony-stimulating factor (G-CSF) at baseline. The primary endpoint was distance walked during the 6-Minute Walk Test (6MWT)

and improvement in the Total Fatigue score on the BarTH Syndrome Symptom Assessment (BTHS-SA).

VI. The TAZPOWER clinical trial was unable to show statistically significant improvements in either 6MWT or total fatigue score of the BTHS-SA as compared to placebo at twelve weeks. There was a high placebo response from the placebo arm in the study which limits the usability and interpretation of endpoints. Furthermore, while the TAZPOWER OLE study was able to show statistical benefit in the above outcomes were reported. Data from a single-arm open label trial is uninterpretable due to potential biases (6MWT being an effort-based assessment).

VII. Subsequently, investigators initiated a natural history study to compare the TAZPOWER OLE cohort (those who reached week 72) to a retrospective external control group to further assess the efficacy of elamipretide (Forzinity) against natural progression of the disease. The natural history control (NHC) arm was taken from patients who attended the 2014, 2016, and/or 2018 Barth Syndrome Foundation International Scientific, Medical and Family Conference. The primary endpoint was distance walked during the 6MWT. Key secondary endpoints included change in baseline in mean muscle strength as assessed by handheld dynamometry (HHD), 5 times sit-to-stand (5XSST) score, SWAY Balance Assessment score, and multi-domain responder index (MDRI).

VIII. While the natural history study was able to show statistical differences in the measured outcomes there are still limitations and unknowns given the trial design. The propensity matching of baseline characteristics for NHC/TAZPOWER participants could not account for all clinical and management variations in individual medical care between patients including prescribed medications, frequency of medical assessments, etc. The efficacy data for the NHC were not collected at the timepoints used for the primary efficacy analysis and the efficacy data for NHC used in the analyses were 100% imputed which could reduce the reliability of predicted values. The trial did not address the remaining questions of the preceding TAZPOWER trials as the study did not assess elamipretide (Forzinity) against a comparator in a prospective clinical trial.

IX. The culmination of evidence is considered low quality given the outcomes assessed were not statistically significant in the randomized controlled trial. Additional open-label trials showed promising results; however, applicability is limited given lack of a comparator arm and observer bias cannot be ruled out. While this is a rare disease state, a samples size of twelve treated individuals may induce biases and limit applicability to larger populations as individual differences may be more pronounced in the dataset. Moreover, the clinical trial program only enrolled patients twelve and older while there is a significant morbidity and mortality risk associated with patients in infancy and early childhood. The utility of elamipretide (Forzinity) in patients under twelve remains unknown and will be confirmed real-world data.

X. After receiving a complete response letter (CRL) in May 2025, Stealth proposed a resubmission for accelerated approval based on the intermediate endpoint of knee extensor muscle strength. In its resubmission, the pharmaceutical manufacturer proposed accelerated approval based on the intermediate endpoint of knee extensor muscle strength, which improved by ~45% in the open-label extension (OLE) of TAZPOWER and correlated with improvements in the 6MWT. The FDA concluded that improvements in knee extension strength were reasonably likely to predict

meaningful clinical benefit, such as an improved ability to stand or walk. However, this endpoint has not been validated to correlate to clinically meaningful improvement or long term clinical impact.

XI. As of November 2025, there is a lack of evidence to support use of this therapy based on two documents of medical and scientific literature in humans. The TAZPOWER clinical trial was unable to show statistically significant improvements in either 6MWT or total fatigue score of the BTHS-SA as compared to placebo in the randomized portion of the trial. Additionally, there was a high placebo response recorded in the randomized portion of the trial which limits the usability and interpretation of endpoints. Endpoints assessed in the TAZPOWER OLE were observational in nature without a comparator. Though natural history data is available, the usability of this data is further limited by the way it was collected given that all data points were imputed. Overall, there is questionable utility of data at present and patients stand to benefit most in the setting of a clinical trial exploring new and emerging treatment options.

XII. Clinical trials limited enrollment to those twelve years of age and older. Data to support the use of elamipretide (Forzinity) in a population younger than twelve has not been established in randomized controlled clinical trials. The utility of therapy in a younger treatment population remains exploratory.

XIII. The most common treatment emergent adverse events (TEAEs) reported for elamipretide (Forzinity) versus placebo, respectively were injection site erythema (100% vs 25%), pain (75% vs 33.3%), induration (66.7% vs 16.7%), pruritis (66.7% vs 16.7%), bronchitis (16.7% vs 8.3%), and ligament sprain (16.7% vs 8.3%). In the OLE portion of the trial TEAEs occurring in 2 or more patients included dizziness (n = 4 [40%]) and nausea (n = 3 [30%]). Three patients had 5 serious AEs of pneumothorax, mucosal inflammation, costochondritis, subcutaneous abscess, and gastroenteritis.

Investigational or Not Medically Necessary Uses

I. Dry age-related macular degeneration (AMD)
   A. Elamipretide (Forzinity) is currently under investigation for the treatment of dry AMD in a phase 3 clinical trial (ReNEW) to evaluate once-daily, SC elamipretide. The primary endpoint is the rate of change in the macular area of photoreceptor loss assessed by spectral domain-optical coherence tomography and ellipsoid zone (EZ) mapping. The Phase 3 trial has an estimated primary completion of August 2026 building on Phase 2 ReCLAIM-2 signals of EZ preservation, despite not meeting its co-primary endpoints (low luminance visual acuity and geographic atrophy progression). Use of elamipretide (Forzinity) in this setting remains investigational.

II. Primary mitochondrial myopathy (PMM)
   A. Elamipretide (Forzinity) was studied for the treatment of PMM in Phase 2 and Phase 3 trials though efficacy data remains . The 24-week, double-blind Phase 3 MMPOWER-3 trial did not meet its co-primary endpoints (6MWT and Primary Mitochondrial Myopathy Symptom

Assessment Total Fatigue) in the overall population. The pharmaceutical company has enrolled for a Phase 3 trial, NuPOWER designed for patients with nDNA PMM based on the nDNA signal seen in MMPOWER-3. This trial is still ongoing and thus use of elamipretide (Forzinity) in this setting remains investigational.

References

1. Thompson WR, Manuel R, Abbruscato A, Carr J, Campbell J, Hornby B, Vaz FM, Vernon HJ. Long-term efficacy and safety of elamipretide in patients with Barth syndrome: 168-week open-label extension results of TAZPOWER. Genet Med. 2024 Jul;26(7):101138.
2. Reid Thompson W, Hornby B, Manuel R, Bradley E, Laux J, Carr J, Vernon HJ. 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 Mar;23(3):471-478.
3. Hornby B, Thompson WR, Almuqbil M, Manuel R, Abbruscato A, Carr J, Vernon HJ. 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.
4. Ferreira C, Pierre G, Thompson R, et al. Barth Syndrome. 2014 Oct 9 [Updated 2020 Jul 9]. In: Adam MP, Feldman J, 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/
5. Cardiovascular and Renal Drugs Advisory Committee. Updated October 18,2024. Available at: https://www.fda.gov/media/182608/download
6. IPD Analytics. Forzinity (elamipretide) New Drug Review. October 8, 2025.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2025