BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

FORZINITY™ (elamipretide) subcutaneous injection Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy**: Forzinity (elamipretide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician, Cardiologist, Geneticist, Hematologist

2. Individual is a male 12 to 35 years of age weighing at least 30 kg

3. Individual has a confirmed diagnosis of **Barth syndrome**, as defined by a pathogenic genetic variant in the *TAZ* gene

ORIGINAL EFFECTIVE DATE: 11/20/2025 | ARCHIVE DATE: | LAST REVIEW DATE: | LAST CRITERIA REVISION DATE:

4. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. Six-minute walk test (6MWT)
    b. Total fatigue score on the Barth Syndrome Symptom Assessment (BTHS-SA) scale
    c. Knee extensor muscle strength measured by handheld dynamometrey

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual is ambulatory but is impaired as assessed by the 6MWT

7. Will not be used in an adult with an estimated glomerular filtration rate less than 30 mL/minute and those undergoing hemodialysis

8. Will not be used in a pediatric patient with renal impairment weighing 30 kg or more

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Forzinity (elamipretide) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician, Cardiologist, Geneticist, Hematologist

2. Individual has documentation of positive clinical response to therapy defined as improvements over baseline in **ALL** of the following
    a. Six-minute walk test (6MWT) of 50 meters
    b. Total fatigue score on the Barth Syndrome Symptom Assessment (BTHS-SA) scale of 1.3
    c. Knee extensor muscle strength measured by handheld dynamometry at least 10% over baseline

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Serious hypersensitivity reactions
    b. Persistent or severe skin reactions

6. Individual is ambulatory but is impaired as assessed by the 6MWT

7. Will not be used in an adult with an estimated glomerular filtration rate less than 30 mL/minute and those undergoing hemodialysis

8. Will not be used in a pediatric patient with renal impairment weighing 30 kg or more

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Description:

Forzinity (elamipretide) is a mitochondrial cardiolipin binder indicated to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg. This indication is approved under accelerated approval based on an improvement in knee extensor muscle strength, an intermediate clinical endpoint, observed in an open-label extension study of Forzinity (elamipretide) that included seven pediatric patients aged 12 years and older. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Forzinity (elamipretide) **is not approved** for use in neonates.

Barth syndrome is a rare X-linked disorder presenting clinically with left ventricular non-compaction, early-onset cardiomyopathy, intermittent neutropenia, abnormal growth patterns, and skeletal myopathy (usually proximal). The condition is attributable to pathogenic variants in *Tafazzin (TAZ)* gene, which encodes a transacylase essential for the final remodeling of cardiolipin (CL). Cardiolipin resides within the inner mitochondrial membrane (IMM), playing crucial roles in mitochondrial integrity and function, including organizing respiratory chain super complexes, preserving cristae architecture, and participating in apoptotic signaling through interactions with cytochrome c. A deficiency in *TAZ* leads to altered cardiolipin composition, marked by an accumulation of monolysocardiolipin (MLCL) and a decrease in cardiolipin, culminating in impaired mitochondrial activity. Forzinity (elamipretide) is a mitochondrial-targeted cardiolipin binder that localizes to the IMM and has been shown to enhance mitochondrial morphology and function.

In the Forzinity (elamipretide) clinical development program summarized in the product label, 12 males aged 12–35 with Barth syndrome received daily 40 mg subcutaneous injections. They participated in a double-blind, placebo-controlled (DBPC) crossover trial: either 12 weeks on Forzinity followed by placebo, or vice versa, with a 4-week washout between periods. Ten completed the DBPC trial and entered open-label extension (OLE) trial, to evaluate long-term safety and tolerability; eight of ten received Forzinity for 168 weeks, and three of eight received Forzinity for 192 weeks.

The *primary endpoints* for the *DBPC trial* were the distance covered during the *6-minute walk test (6MWT)* and the *Total Fatigue Score on the Barth Syndrome Symptom Assessment (BTHS-SA)*. Administration of Forzinity (elamipretide) was **not superior** to placebo with respect to these endpoints. *Knee extensor muscle strength*, assessed via handheld dynamometry, served as a *secondary endpoint* in *both the DBPC and OLE trials*. There was **no increase** in knee extensor muscle strength observed **during** the **DBPC** trial; however, **increases** were documented **during** the **OLE** trial.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Total Fatigue Score on the Barth Syndrome Symptom Assessment (BTHS-SA):
The BTHS-SA is a patient-reported outcome (PRO) questionnaire that assesses symptoms of tiredness, fatigue, and muscle weakness using 8 or 9 questions depending on the version (i.e., adult or adolescent). Each question has 5 response categories scored 1 (not at all), 2 (mild), 3 (moderate), 4 (severe), 5 (very severe). The Forzinity (elamipretide) clinical development program used the total fatigue score (TFS) consisting of responses to the following three questions on the BTHS-SA:

Question 1: Rate your worst feeling of tiredness at rest in the past 24 hours
Question 2: Rate your worst feeling of tiredness during activities in the past 24 hours
Question 4: Rate your worst feeling of muscle weakness in the past 24 hours

The total fatigue score has a range from 3 to 15, with lower scores reflecting less fatigue

Resources:

FORZINITY (elamipretide) product information, revised by Stealth BioTherapeutics, Inc 09-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 16, 2025.

O'Ferrall EK. Mitochondrial myopathies: Clinical features and diagnosis. In: UpToDate, Shefner JM, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated March 24, 2025. Accessed October 16, 2025.

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. Gen Med 2021;23 (3): 471-478; https://doi.org/10.1038/s41436-020-01006-8. Accessed October 16, 2025.

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;17:336 https://doi.org/10.1186/s13023-022-02469-5. Accessed October 16, 2025.

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. Gen Med 2024; 26: doi: https://doi.org/10.1016/j.gim.2024.101138. Accessed October 16, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03098797: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Trial to Evaluate the Safety and Efficacy of Subcutaneous Injections of Elamipretide in Subjects With Genetically Confirmed Barth Syndrome Followed by Open-Label Treatment. Available from: http://clinicaltrials.gov. Last update posted April 04, 2024. Last verified March 2024. Accessed October 16, 2025.