Effective Date **3/1/2025**
Coverage Policy Number **IP0149**

Amyloidosis - Tafamidis Products

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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 the following tafamidis products:

- Vyndamax® (tafamidis capsules)
- Vyndaqel® (tafamidis meglumine capsules)

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, genetic test results, claims records, and/or other information.

Tafamidis products (Vyndamax, Vyndaqel) are considered medically necessary when the following are met:

1. **Cardiomyopathy of Wild-Type or Hereditary Transthyretin Amyloidosis.** Individual meets **ALL** of the following criteria (A, B, C, D and E):
    A. Individual is 18 years of age or older
    B. Documented diagnosis confirmed by **ONE** of the following (i, ii, or iii):
        i. A technetium pyrophosphate scan (i.e., nuclear scintigraphy)
        ii. A tissue biopsy with confirmatory transthyretin (TTR) amyloid typing by mass spectrometry, immunoelectron microscopy or immunohistochemistry
        iii. A transthyretin (TTR) pathogenic variant identified on genetic testing (Examples of TTR mutations include Val122Ile mutation and Thr60Ala mutation. If the patient has wild-type amyloidosis, this is not a TTR mutation)
    C. Diagnostic cardiac imaging has demonstrated cardiac involvement (Examples of cardiac imaging include echocardiogram and cardiac magnetic imaging. Examples of cardiac involvement on imaging include increased thickness of the ventricular wall or interventricular septum.
    D. Individual has heart failure, but does not have New York Heart Association class IV disease
    E. Medication is being prescribed by, or in consultation with, a cardiologist or a physician who specializes in the treatment of amyloidosis

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

Tafamidis products (Vyndamax, Vyndaqel) are considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, examples include reduction in cardiovascular-related hospitalizations, improvement or stabilization in 6-Minute Walk Test, improvement in symptom burden and/or frequency, improvement in quality of life).

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Concurrent use with other medications indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy (e.g., Amvuttra [vutrisiran subcutaneous injection], Attruby [acoramidis tablets], Onpattro [patisiran lipid complex intravenous infusion], Tegsedi [inotersen subcutaneous injection], or Wainua [eplontersen subcutaneous injection]).**
   The requested medication should not be administered in combination with other medications indicated for polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy. Combination therapy is generally not recommended due to a lack of controlled clinical trial data supporting additive efficacy.

2. **Concurrent Use of Vyndaqel and Vyndamax.** There are no data available to support concomitant use.

3. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR)** [Note: For patients with hATTR and cardiomyopathy or mixed phenotype (concurrent cardiomyopathy and polyneuropathy), refer to

FDA-Approved Indication, above]. Neither Vyndaqel nor Vyndamax are indicated for treatment of symptoms of polyneuropathy associated with hATTR.

Background

OVERVIEW

Vyndaqel and Vyndamax are selective stabilizers of transthyretin (TTR) indicated for the treatment of the **cardiomyopathy of wild-type or hereditary TTR-mediated amyloidosis (ATTR-CM)** to reduce cardiovascular mortality and cardiovascular-related hospitalization in adults.[1] Studies excluded patients with New York Heart Association class IV disease.[2]

Disease Overview

In ATTR-CM, there is misfolding of the TTR protein resulting in accumulation of amyloid in the heart causing thickening of both ventricles.[2-8] ATTR-CM may be suspected following cardiac imaging (e.g., echocardiogram, cardiac magnetic imaging). Subsequent testing (e.g., scintigraphy or biopsy) confirms the diagnosis of ATTR-CM. Endomyocardial biopsy confirms the diagnosis of ATTR-CM.[8] Biopsy can confirm if ATTR-CM is due to a hereditary mutant variant of TTR vs. an acquired wild-type variant. In patients with confirmed cardiac amyloidosis, TTR gene sequencing aids in treatment decisions and is necessary for genetic counseling in relatives of patients with a TTR variant.[7] Although many mutations have been identified, mutation of V122I is the most common in the US.[2-6] This mutation is present in 3% to 4% of African Americans and is associated with amyloid cardiomyopathy. Vyndaqel and Vyndamax bind to TTR at the thyroxine binding sites and stabilize the tetramer. This slows dissociation into monomers, which is the rate-limiting step in the amyloidogenic process.[1]

Guidelines

The American Heart Association (AHA) scientific statement for the evolving diagnosis and management of cardiac amyloidosis (2020) recognizes tafamidis as a treatment for ATTR-CM.[7] They note that the benefit of tafamidis has not been observed in patients with NYHA class IV symptoms. Additionally, although combination use of tafamidis with Onpattro® (patisiran lipid complex intravenous infusion) or Tegsedi® (inotersen subcutaneous injection) is appealing to target both TTR silencing and stabilization for the remaining synthesized protein, this approach lacks data and may be cost-prohibitive. Tafamidis should generally be considered the agent of choice in ATTR-CM in patients with reasonable expected survival according to a position statement of the European Society of Cardiology (ESC) working group on myocardial and pericardial disease (2021).[8] The working group notes that tafamidis is the only drug that has shown efficacy in a randomized trial in patients with ATTR-CM and should be considered in patients with reasonable expected survival. The American College of Cardiology (ACC) expert consensus decision pathway on comprehensive multidisciplinary care for patients with cardiac amyloidosis (2023) make similar comments and recommendations to the AHA and ESC regarding tafamidis.[10]

References

1. Vyndaqel and Vyndamax capsules [prescribing information]. New York, NY: Pfizer; October 2023.
2. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016.
3. Maurer MS, Elliott P, Merlini G, et al. Design and rationale of the Phase 3 ATTR-ACT clinical trial (tafamidis in transthyretin cardiomyopathy clinical trial). *Circ Heart Fail*. 2017;10(6).
4. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail.* 2019 Sep;12(9):e006075.
5. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med*. 2017;84(12 Suppl 3):12-26.
6. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21.
7. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.
8. Kittleson MM, Maurer MS, Ambardekar AV, et al; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. AHA scientific statement: cardiac amyloidosis: evolving diagnosis and management. *Circulation.* 2020;142:e7-e22.

9. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC working group on myocardial and pericardial disease. *Eur Heart J.* 2021;42:1554-1568.
10. Kittleson M, Ruberg FL, Ambardekar AV, et al. A report of the American College of Cardiology Solution Set Oversight Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *JACC*. 2023;81(11):1076-1126.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Added "<u>Documentation</u>**: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, genetic test results, claims records, and/or other information." **Cardiomyopathy of Wild-Type or Hereditary Transthyretin Amyloidosis.** The criterion Amyloid deposits are identified on cardiac biopsy was changed to A tissue biopsy with confirmatory TTR amyloid typing by mass spectrometry, immunoelectron microscopy or immunohistochemistry. For diagnosis confirmed by genetic testing, rephrased the term "mutation" to "pathogenic variant." **Conditions Not Covered** Concurrent use with other medications indicated for polyneuropathy of hereditary transthyretin-mediated amyloidosis or transthyretin-mediated amyloidosis-cardiomyopathy (e.g., Amvuttra (vutrisiran subcutaneous injection), Attruby (acoramidis tablets), Onpattro (patisiran lipid complex intravenous infusion), Tegsedi (inotersen subcutaneous injection), or Wainua [eplontersen subcutaneous injection]) was changed to as listed (previously Concomitant Use With Amvuttra (vutrisiran subcutaneous injection), Onpattro (patisiran lipid complex intravenous infusion), Tegsedi (inotersen subcutaneous injection), or Wainua [eplontersen subcutaneous injection]).	3/1/2025

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