Pharmacy Policy Bulletin: J-0936 Transthyretin Amyloid Cardiomyopathy (ATTR-CM) TTR Stabilizers – Commercial and Healthcare Reform	
Number: J-0936	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0936-009	**Original Date:** 08/07/2019
Effective Date: 07/18/2025	**Review Date:** 06/25/2025

Drugs Product(s):	• Attruby (acoramidis) • Vyndaqel (tafamidis meglumine) • Vyndamax (tafamidis)

FDA-Approved Indication(s):	• Attruby (acoramidis)
	  ○ Treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular death and cardiovascular-related hospitalization.
	• Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis)
	  ○ Treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

Background:	• Attruby, Vyndaqel, and Vyndamax bind to and stabilize the transthyretin (TTR) tetramer, slowing dissociation into monomers which is the rate-limiting step in the amyloidogenic process. • ATTR is a rare disease characterized by the aggregation of abnormal deposits of misfolded protein called amyloid. Amyloid deposits most frequently occur in the heart and the peripheral nervous system. Deposits in the heart can cause restrictive cardiomyopathy and progressive heart failure. • There are two types of ATTR-CM. The first is wild type ATTR (ATTRwt) which is not inherited, develops with age, and is associated with misfolding of destabilized native protein. The second is hereditary ATTR (ATTRm) which is inherited and caused by a genetic mutation in the transthyretin gene that causes misfolding of the tetramer subunits. Common mutations in transthyretin gene include *Val122Ile* mutation and *Thr60Ala* mutation. • Liver transplantation is only indicated for hereditary ATTR-CM and generally reserved for patients with early-stage disease associated with *Val30Met* mutations. If amyloid cardiomyopathy is present with significant heart failure, liver transplantation alone is contraindicated and liver-heart transplantation or heart transplantation alone should be considered. Organ transplantation is the only curative option.

- For Attruby and Vyndaqel clinical trials, only patients with NYHA Class I to III were included. However, patients with NYHA Class III failed to show superiority versus placebo in both all-cause mortality and cardiovascular hospitalization frequency. Heart transplant and implantation of a cardiac mechanical assist device were treated as death in the Vyndaqel and Attruby analyses. Combined heart and liver transplant was also treated as death for Vyndaqel analysis.
- The efficacy of Vyndamax was based on a pharmacokinetic study demonstrating no clinically significant differences in steady state maximum concentration (Cmax) and area under the plasma concentration over time curve between Vyndamax and Vyndaqel.
- Two types of amyloid commonly infiltrate the heart: 1) immunoglobulin light-chain amyloid or 2) transthyretin amyloid. Primary (light chain, AL) amyloidosis has cardiac involvement in 50% of cases, other organ involvement can be kidneys, stomach, large intestine, liver, nerves, or skin. It is treated with chemotherapy and steroids.
- There are different types of amyloidosis (e.g., AA (amyloid A) amyloidosis, AL amyloidosis). Bone scintigraphy or heart biopsy detects the type of amyloidosis, and if positive, indicates ATTR amyloidosis. Myocardial amyloid involvement can be visualized by scintigraphic tracers (i.e., ^{99}mTechnetium pyrophosphate). If the scan shows heart to contralateral (H/CL) > 1.5 (or visual Grade 3: uptake greater than rib uptake with mild/absent rib uptake) it is considered ATTR positive and if the H/CL ratio ≤ 1.5 it is considered ATTR negative. If negative, cardiac biopsy remains the gold-standard for amyloid cardiomyopathy and is unlikely to yield false positive or negative findings.
    - Patients with cardiac AL amyloidosis present with negative Tc-99m pyrophosphate (Tc-99m PYP) scintigraphy (absent or mild heart uptake). On the contrary, patients with cardiac amyloidosis transthyretin (ATTR) present with positive Tc-99m PYP scanning (intensive heart uptake). The absence of uptake of bone seeking radiotracers in a patient without myocardial biopsy-proven amyloidosis could mean no disease or AL disease. Tc-99m PYP is readily available in the United States. However, in some cases AL amyloid cardiomyopathy cannot be confidently excluded with Tc-99m PYP, in which case an endomyocardial biopsy and use immunohistochemistry +/- mass spectrometry can provide a definitive diagnosis of ATTR-CM.
- The 6-minute walk test (6MWT) assesses patients with cardiopulmonary disease. It measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes.
- Cardiac function measurements may include New York Heart Association (NYHA) class or echocardiographic global longitudinal strain (GLS). The NYHA functional classification places patients in 1 of 4 categories based on physical activity limitations.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

- Left ventricular (LV) systolic dysfunction is most commonly assessed by echocardiographic ejection fraction (EF) and is widely used as a prognostic

	marker in heart failure. Heart failure with reduced is LVEF < 40%, midrange is LVEF 40% to 49%, and preserved ejection fraction is LVEF ≥ 50%. Echocardiographic GLS detects and quantifies subtle disturbances in LV systolic function by following longitudinal contraction of the myocardium. Mild reduced strain is GLS > 12.6%, moderate reduced strain is 8.1% < GLS < 12.5%, and severe reduced strain is GLS ≤ 8.0%. • The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire to measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life within a 2-week recall period. Overall Summary Score includes the total symptom, physical function, social limitations and quality of life scores. • Cardiac biomarkers are released into the blood when the heart is damaged or stressed. B-type natriuretic peptide and its biologically inert, amino-terminal pro-peptide counterpart (NT-proBNP), and cardiac troponin (T or I) are elevated in ATTR-CM. • Prescribing Considerations: ○ Vyndaqel and Vyndamax share the same active ingredient, but have different salt formulations. Vyndamax and Vyndaqel are not substitutable on a per milligram basis. ○ Vyndaqel or Vyndamax were not studied in patients with estimated glomerular filtration rate less than 25 mL/minute/1.73 m^2 of body-surface area. ○ Efficacy of Vyndaqel or Vyndamax in patients with prior heart and/or liver transplantation or implanted cardiac mechanical assist device has not been established. ○ There are no data to support the safety and efficacy of concomitant use of Attruby, Vyndaqel, or Vyndamax and TTR-lowering agents (Amvuttra [vutrisiran], Onpattro [patisiran], Tegsedi [inotersen]). Additionally, clinical trials for Onpattro and Tegsedi did not allow for concomitant use of tafamidis.

Approval Criteria

I. Initial Authorization

When a benefit, coverage of Attruby, Vyndaqel, or Vyndamax may be approved when all of the following criteria are met **(A. through E.)**:

A. The member is 18 years of age or older.

B. The product is prescribed by or in consultation with a cardiologist or physician who specializes in the treatment of amyloidosis.

C. The prescriber submits clinical documentation supporting cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) diagnosis (no ICD-10 code) including both of the following **(1. and 2.)**:

1. The member meets one (1) of the following criteria **(a. or b.)**:

a. Amyloid deposits on cardiac biopsy

b. Scintigraphy with radiotracers (for example, technetium pyrophosphate) and one (1) of the following **(i. or ii.)**:

a. Heart to lung contralateral > 1.5 (grade 3)

b. Heart to lung visual contralateral grade 2 to 3

2. The member has cardiac involvement supported by one (1) of the following tests **(a., b., or c.)**:

a. Cardiac magnetic resonance

b. Echocardiography

c. Serum cardiac biomarker (for example, B-type natriuretic peptide, cardiac troponin)

D. The member has New York Heart Association (NYHA) Class I, II, or III.

E. The member is not simultaneously utilizing transthyretin-lowering agents other than the requested drug (for example, Amvuttra, Attruby, Vyndaqel, Vyndamax, Onpattro, or Wainua).

II. Reauthorization

When a benefit, reauthorization of Attruby, Vyndaqel, or Vyndamax may be approved when all of the following criteria are met **(A. and B.)**:

A. The prescriber documents that the member has experienced disease improvement or delayed disease progression from baseline in one (1) of the following **(1. through 5.)**:
  1. 6-minute walk test
  2. Cardiac function (for example, global longitudinal strain, LVEF, NYHA class)
  3. Kansas City Cardiomyopathy Questionnaire-Overall Summary
  4. Number of cardiovascular-related hospitalizations
  5. Serum cardiac biomarker (for example, B-type natriuretic peptide, cardiac troponin)

B. The member is not simultaneously utilizing transthyretin-lowering agents other than the requested drug (for example, Amvuttra, Attruby, Vyndaqel, Vyndamax, Onpattro, or Wainua).

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. The member does not have primary (light chain) amyloidosis.

II. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

III. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None.

References:

1. Attruby [package insert]. Palo Alto, CA: BridgeBio Pharma, Inc.; November 2024.
2. Vyndaqel and Vyndamax [package insert]. New York, NY: Pfizer Inc.; October 2023.
3. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(11):1076-1126.
4. Ruberg, FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. *Circulation*. 2012;126(10): 1286–1300.
5. American Society of Nuclear Cardiology. Diagnose, Differentiate, and Manage Cardiac Amyloidosis. Available at: https://www.asnc.org/cardiacamyloidosis. 2019. Accessed July 15, 2019.
6. American Heart Association. Classes of Heart Failure. Available at: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure. 2019. Accessed July 15, 2019.

7. Park JJ, Park JB, Park JH, Cho GY. Global Longitudinal Strain to Predict Mortality in Patients with Acute Heart Failure. *J Am Coll Cardiol.* 2018;71(18):1947-1957.