Amyloid Cardiomyopathy

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO064

Description

Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), and tafamidis (Vyndamax) are orally administered transthyretin stabilizers.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
acoramidis (Attruby)	Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis	356 mg tablets	112 tablets/28 days
tafamidis meglumine (Vyndaqel)		20 mg capsules	120 capsules/30 days
tafamidis (Vyndamax)		61 mg capsules	30 capsules/30 days

Initial Evaluation

I. **Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), or tafamidis (Vyndamax)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a cardiologist; **AND**
   C. Medication will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e., inotersen (Tegsedi), patisiran (Onpattro), eplontersen (Wainua), acoramidis (Attruby), tafamidis meglumine (Vyndaqel), tafamidis (Vyndamax)]; **AND**
   D. A diagnosis of **cardiomyopathy of wild type (wATTR-CM) or hereditary transthyretin-mediated amyloidosis (hATTR-CM)** when the following are met:
      1. Provider attestation a monoclonal protein screening shows a normal serum kappa/lambda free light chain ratio (<0.26 or >1.65) and no presence of serum/urine immunofixation is detected; **AND**
         i. Prescence of transthyretin precursor protein confirmed by scintigraphy (i.e., radiotracer 99m technetium pyrophosphate (99mTc-PYP); **OR**
         ii. Documented presence of amyloid deposit by endomyocardial biopsy; **AND**
      2. Provider attestation of history of heart failure evidenced by at least one prior hospitalization for heart failure or clinical evidence of heart failure such as volume overload, elevated intracardiac pressures, heart failure symptoms requiring management with a diuretic; **AND**

3. New York Heart Association (NYHA) functional class I-III; **AND**
4. No prior history of liver or heart transplantation

II. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are considered not medically necessary when used for all other conditions, including but not limited to:
   A. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV

III. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are considered investigational when used for all other conditions, including but not limited to:
   A. Polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTR-PN) or familial amyloid polyneuropathy (FAP)
   B. Primary (light chain) amyloidosis

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 that the patient has experienced a positive clinical response therapy (e.g., reduced cardiovascular hospitalizations, improved quality of life, slowing of disease progression, etc.); **AND**
IV. No prior history of liver or heart transplantation; **AND**
V. New York Heart Association (NYHA) functional class I-III; **AND**
VI. Medication will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e., inotersen (Tegsedi), patisiran (Onpattro) eplontersen (Wainua), acoramidis (Attruby), tafamidis meglumine (Vyndaqel), tafamidis (Vyndamax)].

Supporting Evidence

I. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), and tafamidis (Vyndamax) are transthyretin (TTR) stabilizers FDA approved for the treatment of cardiomyopathy (CM) of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
II. Given the complexity of diagnosis and treatment of ATTR-CM, therapy should be prescribed by, or in consultation with, a cardiologist.
III. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a restrictive heart disease caused by extracellular deposits of amyloid fibrils, clumps of misfolded TTR proteins which normally

circulate through the body carrying retinol (vitamin A) and thyroxine. This condition results in heart failure, usually with a preserved ejection fraction, due to walls of the heart stiffening and preventing the heart from filling properly. Shortness of breath, arrhythmias, and death are all results of the disease. There are two types of ATTR-CM, hereditary (hATTR-CM), sometimes called variant, and wild type (wATTR-CM). Hereditary cases are due to a variant in the TTR gene, with symptoms presenting as early as the 30s, and more commonly affects African Americans in the United States with one in 25 Black individuals having the gene variant. Wild type does not include the gene mutation and makes up about 90% of all cases of ATTR-CM, and while it affects the heart, it can also cause carpal tunnel syndrome and peripheral neuropathy, mainly affecting elderly men regardless of any one race, with an average age of 74 years at diagnosis. Historically, considered a rare disease, advancements in cardiac imaging and better understanding of the TTR gene have led to 5,000-7,000 new cases identified per year. A conservative estimate suggest that 50,000 to 150,000 adults in the US have ATTR-CM. Life expectancy for untreated patients with ATTR-CM is about two to five years after diagnosis.

IV. Cardiomyopathy (CM) of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) should be suspected in all elderly patients with recurrent HF exacerbations, irrespective of their ejection fraction status. Often, patients will present with fatigue, poor exercise tolerance, and shortness of breath with the New York Heart Association (NYHA) functional class I to III. In addition, patients may have significant right ventricular involvement, causing peripheral congestive symptoms like elevated jugular venous pressure, lower extremity edema, hepatic congestion, and ascites. Those with wATTR-CM additionally develop extracardiac symptoms due to nerve entrapment with amyloid deposits. Bilateral carpal tunnel syndrome and lumbar spinal stenosis are commonly associated with wATTR-CM, and often occur five to ten years before a diagnosis of ATTR-CM occurs.

V. The cardiac amyloidosis diagnostic process begins with clinical history, electrocardiogram (ECG), and transthoracic echocardiogram. Echocardiographic clues can also rule out other causes of heart failure (HF), but it is not diagnostic to ATTR-CM alone. The 2022 American Heart Association also notes that patients may undergo cardiovascular magnetic resonance (CMR) imaging which can further identify amyloidosis with sensitivity and specificity of 85 to 90%, but cannot distinguish between light chain amyloidosis heart failure (AL-CM) and ATTR-CM. If the above is consistent with cardiac amyloidosis, monoclonal protein tests are performed. Patients who test positive for serum/urine immunofixation electrophoresis (IFE) and have a serum kappa/lambda free light chain abnormality, should be further screened for AL-CM as treatment in conjunction with a hematologist should begin as soon as possible. If the protein test is negative, cardiac scintigraphy with technetium pyrophosphate (Tc-PYP) is preformed, with a positive test indicative of ATTR-CM. Patients may also elect to undergo genetic testing to see if positive for the gene variation due to high likelihood of familial inheritance of the gene mutation. A diagnostic pitfall would be to interpret a cardiac scintigraphy scan without a concomitant monoclonal protein screen; a scintigraphy scan alone is neither appropriate nor valid for distinguishing ATTR-CM from AL-CM. An endomyocardial biopsy with congo red

staining, has a sensitivity and specificity of 100%, and remains the gold standard to diagnose ATTR-CM, but patients and physicians may prefer the other less invasive measures for confirmation such as scintigraphy.

VI. There are no guidelines specific to ATTR-CM in the U.S.; however, the American Heart Association (2022) and American College of Cardiology (2023) have recommendations for the treatment of hATTR-CM and wATTR-CM. Currently only the TTR stabilizer, tafamidis (Vyndamax/Vyndaqel) is noted as first line use in cardiomyopathy on top of standard of care HF medications (e.g. diuretics, beta-blockers) and anti-arrhythmics. The guidelines have not been updated to include acoramidis (Attruby). The guidelines do not comment on using other TTR agents in combination, such as TTR silencers with TTR stabilizers. Clinical trial programs for acoramidis (Attruby) and tafamidis (Vyndamax/Vyndaqel) did not study these medications in combination with TTR silencers, therefore such use would not be appropriate due to lack of safety and efficacy data supporting such a treatment approach (i.e., in combination with inotersen (Tegsedi), patisiran (Onpattro), and/or eplontersen (Wainua)). Additionally, use of tafamidis (Vyndamax/Vyndaqel) in combination with acoramidis (Attruby) is not permitted as combination treatment is not expected to result in greater efficacy or better patient outcomes, as demonstrated in the ATTRibute-CM clinical trial.

tafamidis (Vyndamax/Vyndaqel)

I. Tafamidis meglumine (Vyndaqel) was studied in a Phase 3, multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (ATTR-ACT trial). Patients included in the pivotal trial had a history of heart failure, evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm and confirmed transthyretin-mediated amyloidosis by documented presence of amyloid deposit by biopsy and/or presence of transthyretin precursor protein confirmed by scintigraphy. Patients were excluded if they had NYHA Class IV heart failure, primary amyloidosis, or a history of liver or heart transplantation. Patients on average were 74 years of age, 90% male, with wild-type TTR (65%); they were randomized 1:2:2: to tafamidis 20mg, 80mg, or placebo once daily.

II. The trial met its primary endpoint, demonstrating a significant reduction (p=0.0006) in all-cause mortality and frequency of cardiovascular-related hospitalizations (p<0.0001) in the pre-specified pooled tafamidis meglumine (Vyndaqel) 20-mg and 80-mg groups versus placebo at 30 months. Tafamidis meglumine (Vyndaqel) also showed a lower rate of decline in distance for the 6-minute walk test and lower rate of decline in the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS). Of note, subgroup analysis of patients identified as NYHA class III at baseline did not show a reduction in all-cause mortality or cardiovascular related hospitalizations. In NYHA class III patients, cardiovascular related hospitalizations were actually higher among patients receiving tafamidis meglumine (Vyndaqel) than those receiving placebo.

III. Tafamidis meglumine (Vyndaqel) was studied as monotherapy. There is no data on the use of combination therapy with other medications indicated for different types of amyloid disease.

IV. Within the pivotal trial results, a greater proportion of patients in the tafamidis meglumine group either improved upon or remained at their respective NYHA baseline classification compared with patients in the placebo group.

V. Vyndamax (tafamidis) was developed for patient convenience. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are not substitutable on a per-mg basis.

acoramidis (Attruby)

I. The safety and efficacy of acoramidis (Attruby) was studied in a Phase 3, randomized, double-blind, placebo-controlled study (ATTRibute-CM) that ran for 30 weeks. A total of 632 adult patients were randomized 2:1 to receive acoramidis (N=421) 800 mg twice daily or matching placebo (n=211) on top of standard heart failure medications (e.g., diuretics 93%, beta-blockers 57%). On average, patients were aged 77 years, White (87%), male (90%), with wild-type TTR (90%), and New York Heart Association (NYHA) class II (69.6%). Due to a protocol amendment post the approval of tafamidis (Vyndamax/Vyndaqel) patients were allowed to begin tafamidis (Vyndamax/Vyndaqel); 61 patients (15.9%) in the acoramidis (Attruby) arm and 46 in the placebo arm (22.8%) were on tafamidis (Vyndamax/Vyndaqel) plus the respected study arm agent. Patients were required to be on 12 months of single arm study agent before allowance of tafamidis (Vyndamax/Vyndaqel) and average exposure of tafamidis (Vyndamax/Vyndaqel) was 11 months. Patients with NYHA Class IV and chronic kidney disease (CKD) stage IV were excluded from the study. The primary endpoint was a four-step hierarchical test that included: death from any cause (which was defined in the trial as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device), cumulative frequency of cardiovascular-related hospitalization (CVH), the change from baseline in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in the 6-minute walk distance in the modified intent to treat (mITT) population, those with an estimated glomerular filtration rate (eGFR) ≥30 ; analyzed using the Finkelstein-Schoenfeld Method of wins versus losses on matched pair tests.

II. The primary analysis met statistical significance in the percent number of wins versus placebo; 63.7 with acoramidis (Attruby) versus 35.9 with placebo, a win ratio of 1.8 (95% CI:1.4-2.2), p<0.001.

- Furthermore, all cause-mortality (ACM) and cardiovascular related hospitalizations (CVH) sub-composite met statistical significance, with hazard ratio (HR) of 0.645 (95%CI: 0.500-0.832, p=0.0008). This indicates a 35% risk reduction for ACM and CVH associated with acoramidis (Attruby).
- Additional individual components of the hierarchical composite that were statistically significant in favor of acoramidis (Attruby) versus placebo were reduction of CVH, improvement in NT-proBNP levels, and changes in 6MWD.

- The ACM component by itself was not statistically significant in the modified intention to treat (mITT) population, with 19.3% versus 25.7% of patients achieving this endpoint in the acoramidis (Attruby) vs placebo arm and a relative risk reduction (RRR) of 25% in favor of acoramidis (Attruby) p=0.057. However, ACM evaluated in the intention to treat (ITT) population (prespecified secondary endpoint) which included patients with eGFR of 15-30, was statistically significant, with 20.0% of patients in the acoramidis (Attruby) arm reaching this endpoint versus placebo at 27.0%, p=0.039.
- Secondary outcomes included health-related quality of life assessment utilizing the KCCQ-OS questionnaire. The results was -11.48 in the acoramidis (Attruby) arm versus -21.42 in placebo, difference of 9.94 [5.19-14.10] p<0.0001.
- Sensitivity analyses indicated that receiving tafamidis (Vyndamax/Vyndaqel) with acoramidis (Attruby) showed no additional benefit.

III. Upon completion of ATTRibute-CM, 389 patients enrolled in the open-label extension study. Continuous use of acoramidis (Attruby) was associated with sustained clinical benefits at month 42, with HR for all-cause mortality of 0.64.

IV. The overall quality of evidence for acoramidis (Attruby) is considered moderate. ATTRibute-CM demonstrated statistically significant and clinically meaningful benefits in favor of acoramidis (Attruby) when evaluating the primary endpoint (composite) and select hierarchical components. Most importantly, all-cause mortality (ITT population only) and cardiovascular related hospitalizations risk was reduced with acoramidis (Attruby) treatment by 35%. While all-cause mortality alone was not statistically significant at the end of 30 months in the modified intent to treat group, this may be due to the relative short-term study time frame and a healthier overall population at baseline. Real world applications to excluded populations, such as those with NYHA class IV symptoms, are unknown at this time.

Investigational or Not Medically Necessary Uses

I. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV
   A. In both the ATTR-ACT trial and ATTRibute-CM trial, patients with NYHA Class IV were excluded from the pivotal trial. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine and acoramidis treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) and acoramidis (Attruby) may be less effective once amyloid deposition has caused irreversible organ damage.

II. Polyneuropathy of hereditary transthyretin-mediated amyloidosis or familial amyloid polyneuropathy (FAP)

A. Coelho et al. 2012 reported no significant changes in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP) as coprimary endpoints were not met in the ITT population.
B. The US FDA did not approve tafamidis meglumine (Vyndaqel) use in FAP during a filing in 2012, due to limited efficacy data. The agency requested the completion of a second efficacy study to establish substantial evidence of effectiveness prior to approval.

III. Primary (light chain) amyloidosis
A. In both pivotal trials, patients with primary amyloidosis were excluded. Primary amyloidosis is caused by a bone marrow disorder. Treatment consists of chemotherapy or bone marrow transplant.

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
eplontersen (Wainua)	Hereditary transthyretin-mediated amyloidosis with polyneuropathy
inotersen (Tegsedi)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Reformatting to align with new policy format. Addition of acoramidis (Attruby) for indication of ATTR-CM. Expansion of heart failure definition in initial criteria. Addition of monoclonal protein screening to initial criteria. Updates to supportive evidence section.	02/2025
Policy created	08/2019