Acoramidis (ATTRUBY) in Transthyretin Amyloid Cardiomyopathy (ATTR-CM)
National Drug Mini-Monograph
June 2025

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Transthyretin (TTR) stabilizer
Indication Under Review[1]	Treatment of cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) to reduce CV death and CV-related hospitalization
Dosage Regimen	712 mg (2 x 356 mg tablets) orally twice daily, with or without food; tablets must be swallowed whole
Dosage Forms Under Review	356 mg oral tablets

EFFICACY CONSIDERATIONS

Trial	**ATTRibute-CM**
Design	Phase 3, multinational, double-blind, randomized, placebo-controlled
Population	N=611 (MITT); adults with diagnosis of ATTR-CM and clinical heart failure • ATTR-CM diagnosis based on endomyocardial biopsy with confirmatory typing or positive results (Perugini grade ≥2) on technetium-99m scintigraphy combined with biochemical exclusion of light chain (AL) amyloidosis • Clinical heart failure determined by ≥1 prior heart failure hospitalization, signs and symptoms of volume overload, or heart failure requiring diuretic treatment. • Key inclusion criteria: 6MWD ≥150m, NT-proBNP ≥300 pg/mL, LV wall thickness ≥12 mm • Key exclusion criteria: ACS, coronary revascularization, CVA/TIA in past 90 days; elevated transaminases >2x ULN or total bilirubin >3x ULN; NT-proBNP ≥8500 pg/mL; eGFR <15 mL/1.73m^2 BSA. • Of note, tafamidis treatment was permitted after the initial 12 months
Intervention	2:1 randomization to acoramidis 712 mg twice daily or placebo for 30 months Primary endpoint: hierarchical efficacy analysis of all-cause death, CV hospitalization, change from baseline NT-proBNP, change from baseline in 6MWD expressed as win ratio
Baseline/ Demographics	77 yrs mean age; 90% male; 88% White; 90% wild-type ATTR-CM; 72% NYHA HF functional class II; 17% NYHA HF functional class III; 2872 ng/L mean NT-proBNP; 78% completed trial Concomitant tafamidis: 14.9% acoramidis vs. 23% placebo pts (median time to start- 17 mos)
Results	• Primary hierarchical composite endpoint of all-cause death, CV hospitalization, NT-proBNP change from baseline, and 6MWD change from baseline favored acoramidis vs. placebo, with a Win ratio of 1.77 (96% CI 1.4 – 2.2; p <0.0001). • The FDA review (and subsequent labeling) focused on two components of the primary endpoint: all-cause death and CV hospitalization. Acoramidis was associated with a 36% reduction in the composite of all-cause death or CV hospitalization (hazard ratio: 0.65; 95% CI 0.50-0.83), driven by reduction in CV hospitalization. In a post hoc analysis, Kaplan-Meier curves separated at 3 months favoring acoramidis and continued through 30 months. • All-cause mortality: 79% events were CV-related. Prespecified sensitivity analysis of death from any cause was not statistically significant. A favorable trend of survival benefit occurred at about 19 months. • CV hospitalization: Relative risk ratio was 0.50 (95% CI 0.36-0.70).

Selected endpoints

30-month endpoints	ACOR (n=409)	PBO (n=202)
All-cause mortality	19%	26%
CV hospitalization	27%	43%

- Acoramidis was associated with less decline from baseline in 6MWD (LS mean difference of 40 meters) and health status assessed by KCCQ-OS (LS mean difference of 10 points) vs. placebo.
- Potential impact of concomitant tafamidis use: Given the small number of events in the subgroup of patients receiving tafamidis, post hoc analysis of data is inconclusive.
- Open label extension study through 42 months suggests sustained effect of acoramidis.

SAFETY CONSIDERATIONS

Boxed Warnings None

Contraindications None

Other Warnings None

Top AEs

	Acoramidis N=421	Placebo N=211
Overall adverse events	98.1%	97.6%
Gastrointestinal	11.6%	7.6%
Upper abdominal pain	6.5%	1.4%
Discontinuations due to AEs	9.3%	8.5%

- Other: Increases in serum creatinine (mean 0.2 mg/dL) and decreases in estimated glomerular filtration rate (eGFR) (mean -8.2 mL/min/1.73 m^2) were observed with acoramidis treatment, generally within 4 weeks of initiation. Changes were reversible upon discontinuation of acoramidis.

Drug Interactions

- UGT inducers and strong CYP3A inducers may reduce acoramidis exposure. Avoid acoramidis with UGT inducers and strong CYP3A inducers.
- CYP2C9 substrate exposure may be increased with co-administration of acoramidis. More frequent monitoring may be needed when acoramidis is administered with sensitive substrates of CYP2C9.

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	Comments
Acoramidis (ATTRUBY)	TBD	TBD	ATTR-CM	TTR stabilizer 712 mg (356 mg x2 tabs) twice daily
Tafamidis meglumine (VYNDAQEL)	Yes	Yes	ATTR-CM	TTR stabilizer 80 mg (20 x4 caps) once daily or 20 mg once daily (off-label dose)
Tafamidis (VYNDAMAX)	Yes	Yes	ATTR-CM	TTR stabilizer 61 mg cap once daily (equiv to 80 mg meglumine)
Vutrisiran (AMVUTTRA)	Yes	Yes Pending	ATTR-PN ATTR-CM	TTR silencer (small interfering RNA agent) 25 mg subcutaneous every 3 months

HA PLACE IN THERAPY	**Potential Use in VHA**	• Cardiac amyloidosis is a rare disease that occurs when amyloid fibrils are formed from misfolded proteins and deposit into the myocardial interstitium. ATTR-CM may occur in the presence (variant type) or absence (wild type) of a genetic mutation. ATTR-CM typically causes a restrictive CM. In addition to heart failure, other cardiac symptoms include conduction disturbances and atrial fibrillation. Median survival in untreated patients is about 3 to 6 years. The true prevalence of ATTR-CM is unknown but is suspected to be underrecognized. Extracardiac manifestations such as musculoskeletal symptoms, polyneuropathy, and autonomic dysfunction may also occur. • Acoramidis is a the second TTR stabilizer approved by the FDA for the treatment of ATTR-CM to reduce CV death and CV hospitalization. Tafamidis, the first TTR stabilizer, was approved in 2019. Vutrisiran is a TTR silencer approved by FDA for ATTR-CM in 2025. • Evidence from the ATTRibute-CM trial showed that acoramidis was more effective than placebo in reducing the composite endpoint of CV hospitalization and all-cause death, driven by a reduction in CV hospitalization. Appearance of benefit occurred at about 3 months and continued through treatment. • Overall, the occurrence of adverse events with acoramidis vs. placebo was similar. Acoramidis was associated with an excess of gastrointestinal adverse events vs placebo, though most adverse events were considered mild. • There are no head-to-head trials comparing acoramidis to tafamidis or vutrisiran. In ATTRibute-CM, tafamidis treatment was permitted after 12 months. Post hoc analysis of the subgroup of patients receiving tafamidis are inconclusive. • The Institute for Clinical and Economic Review (ICER) conducted a comparative review of the three disease modifying agents for ATTR-CM (acoramidis, tafamidis, vutrisiran). Compared with no treatment, ICER determined that there is a high certainty of small net benefit and moderate certainty of substantial net benefit with acoramidis vs. no treatment in a contemporary ATTR-CM population. There is insufficient evidence to compare the net health benefits of the three agents.

Abbreviations: 6MWD=6 minute walk distance; ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; CVA=cerebrovascular accident; HF=heart failure; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Summary score; LS=least square; MITT=modified intention to treat; NYHA=New York Heart Association; TIA=transient ischemic attack

References

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