Vutrisiran (AMVUTTRA) 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	RNA interfering agent that causes degradation of hereditary and wild type transthyretin (TTR), which results in lowering of serum TTR and TTR protein deposits in tissues
	Indication Under Review[1]	Treatment of cardiomyopathy of hereditary or wild-type TTR-mediated amyloidosis (ATTR-CM) to reduce cardiovascular (CV) death, CV hospitalization, and urgent heart failure visits *(Note: Vutrisiran is also indicated for the treatment of polyneuropathy (PN) in hereditary ATTR.)*
	Dosage Regimen	25 mg subcutaneous injection once every 3 months into abdomen, thighs, or upper arms; administered by healthcare professional
	Dosage Forms Under Review	25 mg per 0.5 mL solution for injection supplied in a single dose, prefilled 1 mL syringe; stored at room temperature

EFFICACY CONSIDERATIONS		
	Trial	**HELIOS-B**
	Design	Phase 3, international, double-blind, randomized, placebo-controlled
	Population	N=655 adults with diagnosis of ATTR-CM (wild-type or variant) and clinical heart failure • ATTR-CM diagnosis based on tissue biopsy or validated scintigraphy-based diagnosis of ATTR-CM in the absence of monoclonal gammopathy; evidence of cardiac involvement by echo and end diastolic interventricular septal wall thickness greater than 12 mm • 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 ≥150 m, NT-proBNP >300 pg/mL and <8,500 pg/mL • Key exclusion criteria: NHYA class IV (or NYHA class III with Amyloidosis Disease Stage 3); CM not due to ATTR amyloidosis; eGFR <30 ml/min per 1.73 m^2; polyneuropathy disability (PND) Score IIIa, IIIb, or IV (requires assistance to walk or wheelchair bound) at screening; elevated transaminases >1.5x ULN or total bilirubin >1.5x ULN; eGFR <30 mL/1.73m^2; recent ACS or unstable angina; • Of note, tafamidis treatment was permitted at baseline and during the trial
	Intervention	1:1 randomization to vutrisiran 25 mg subcutaneously every 12 weeks for 33-36 mos; all patients instructed to take the recommended daily allowance of vitamin A • Primary endpoint: composite of all-cause death and recurrent CV events defined as CV hospitalization or urgent visits for HF • All endpoints analyzed in overall population and in monotherapy population (no tafamidis at baseline)
	Baseline/ Demographics	77 yrs mean age; 92% male; 85% White; 88% wild-type ATTR; NYHA class II (78% overall population, 87% monotherapy population); NYHA class III (9% overall population, 7% monotherapy population); 77% and 70% completed treatment in vutrisiran and placebo groups, respectively Concomitant tafamidis: 40% use at baseline; 22% of pts in monotherapy group initiated tafamidis during the trial (at a median of 17 mos) SGLT2: 33% of patients started SGLT-2 inhibitors during the trial
	Results	• Primary composite endpoint of all-cause death and recurrent CV events: vutrisiran superior to placebo in overall population and monotherapy population

Primary Endpoint	Overall population			Monotherapy population		
Up to 36 months	**VUT N=326 %**	**PBO N=328 %**	**Hazard ratio**	**VUT N=196 %**	**PBO N=199 %**	**Hazard ratio**
All-cause death or recurrent CV events (Pts with ≥1 event)	38	48	0.72 (0.56-0.93)	39	53	0.67 (0.49-0.93)
All-cause death	16	21	0.69 (0.49-0.98)	18	23	0.71 (0.47-1.06)
Recurrent CV events	34	41	0.73 (0.61-0.88)	34	44	0.68 (0.53-0.86)

- Vutrisiran was associated with less decline from baseline in 6MWD (LS mean difference of 27 meters in overall population and 32 meters in monotherapy population) and health status assessed by KCCQ-OS (LS mean difference of 5.8 points in overall population and 8.7 points in monotherapy population) vs. placebo.
- All-cause death in the open label extension study at 42 months was significantly lower with vutrisiran vs. placebo (HR 0.65, 95% CI 0.46-0.90 in overall population; HR 0.66, 95% CI 0.44-0.97).

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	**Reduced serum vitamin A levels:** Vutrisiran causes a reduction in serum vitamin A levels. Supplementation of the recommended daily allowance of vitamin A is advised with vutrisiran treatment. Patients should be referred to an ophthalmologist if ocular symptoms of vitamin A deficiency occur.
Top AEs	• Patients reporting ≥1 AE: 99% vutrisiran vs. 98% placebo; no excess of specific AEs with vutrisiran • Discontinuations due to AEs: 3% vutrisiran vs. 4% placebo • Other: no clinically relevant changes in laboratory measures, vital signs, or electrocardiograms
Drug Interactions	• Vutrisiran is not expected to cause drug interactions by enzyme induction or modulating drug transporters; no clinical drug interaction studies have been performed.

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	Comments
Vutrisiran (AMVUTTRA)	**Yes**	**Yes**	**ATTR-PN ATTR-CM**	**TTR silencer (small interfering RNA agent) 25 mg subcutaneous every 3 months**
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)

VHA 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 results from the misfolding of TTR proteins and 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. • Vutrisiran is the first RNA silencer approved for ATTR-CM in the U.S. Vutrisiran is also FDA approved for the treatment of polyneuropathy of hereditary ATTR. Alternative ATTR-CM disease modifying treatments available in the U.S. are the TTR stabilizers tafamidis and acoramidis. • Evidence from the HELIOS-B trial showed that vutrisiran reduced the risk of the composite endpoint of all-cause death and recurrent CV events in the overall population vs placebo. The benefit of vutrisiran was also shown when the components were analyzed individually. In the monotherapy population (those patients not on tafamidis at baseline), similar benefits of vutrisiran were shown for the composite endpoint and recurrent CV events alone. Vutrisiran was associated with less decline in functional status and quality of life considered to be clinically meaningful vs. placebo. • The occurrence of adverse events with vutrisiran vs. placebo was similar in HELIOS-B. Vutrisiran causes reduced vitamin A levels. Supplementation of vitamin A is necessary. • There are no head-to-head trials comparing vutrisiran to acoramidis or tafamidis. Forty percent of patients in HELIOS-B were on tafamidis at baseline, and an additional 22% of patients initiated tafamidis during the trial; however, the trial was not powered to show differences within this subgroup. • The Institute for Clinical and Economic Review (ICER) conducted a comparative review of the three disease modifying agents for ATTR-CM (acoramidis, tafamidis, vutrisiran). ICER determined that there is a high certainty of substantial net benefit with vutrisiran vs. no treatment or in addition to tafamidis 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; NYHA=New York Heart Association; TIA=transient ischemic attack

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References

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