

AMVUTTRA™ (vutrisiran)

Product Fact Sheet

- AMVUTTRA is approved for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.
- hATTR amyloidosis is a rare, underdiagnosed, inherited, rapidly progressive, debilitating and fatal disease caused by variants in the transthyretin (TTR) gene that result in misfolded TTR protein accumulating as amyloid deposits in multiple tissues including the nerves, heart and gastrointestinal tract.¹⁻⁴
- AMVUTTRA is an RNAi (RNA interference) therapeutic that harnesses the body's natural process to silence TTR messenger RNA and reduce the production of TTR in the liver, which results in a reduction of serum TTR protein and the amount of amyloid deposits in tissues.
- AMVUTTRA uses an Enhanced Stabilization Chemistry-GalNAc conjugate, designed for high metabolic stability, resulting in increased potency and prolonged duration of activity to allow infrequent dosing.⁵
- AMVUTTRA is a subcutaneous injection administered by a healthcare professional once every three months.
- The FDA approval of AMVUTTRA was based on positive 9-month results from the HELIOS-A Phase 3 trial, where AMVUTTRA demonstrated the potential to halt the progression of or reverse the polyneuropathy of hATTR amyloidosis and improved other key measures of disease burden relative to external placebo.⁶
 - In HELIOS-A, AMVUTTRA met all primary and secondary endpoints at 9 months.⁶
- AMVUTTRA demonstrated an encouraging safety and tolerability profile through 9 months of treatment.⁶
 - The most common adverse reactions were arthralgia, dyspnea and vitamin A decreased.
- For more information about AMVUTTRA, please visit AMVUTTRA.com.

AMVUTTRA Clinical Profile at a Glance⁶

- The FDA approval of AMVUTTRA was based on positive 9-month results from the global, randomized, open-label, multicenter Phase 3 HELIOS-A study that evaluated the efficacy and safety of AMVUTTRA across a diverse group of adult patients with hATTR amyloidosis with polyneuropathy. The efficacy of AMVUTTRA was assessed by comparing the AMVUTTRA group in HELIOS-A with the placebo group from the APOLLO Phase 3 study of patisiran, a randomized controlled study in a comparable patient population.
 - AMVUTTRA met the primary endpoint showing improvement in the modified Neuropathy Impairment Score (mNIS+7), which assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure.
 - Patients treated with AMVUTTRA experienced a 2.2 point mean decrease (improvement) from baseline, compared to a 14.8 point mean increase (worsening) reported for the external placebo group, resulting in a 17.0 point mean difference relative to placebo.
 - The majority of patients treated with AMVUTTRA experienced reversal in neuropathy impairment from baseline (<0 change from baseline in mNIS+7 score).

- AMVUTTRA™ met all secondary endpoints at 9 months, demonstrating improvement in quality of life as assessed by the Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) instrument and in gait speed as assessed by the timed 10-meter walk test (10-MWT), both compared to the external placebo group.
 - o AMVUTTRA treatment resulted in a 3.3 point mean decrease (improvement) in Norfolk QoL-DN score from baseline at 9 months as compared to a 12.9 point mean increase (worsening) reported for the external placebo group, resulting in a mean 16.2 point difference relative to placebo.
 - o Patients treated with AMVUTTRA remained stable in gait speed (mean decrease of 0.001 meters/second in 10-MWT), compared with patients in the external placebo group who demonstrated worsening (mean decrease of 0.133 meters/second in 10-MWT).
- In addition, improvements in exploratory endpoints were observed with AMVUTTRA, including improvement in modified body mass index (mBMI) relative to external placebo.
- At 9 months, AMVUTTRA achieved a rapid, powerful and sustained reduction in serum TTR levels, with an 83 percent mean serum TTR reduction.
- In HELIOS-A, no drug-related discontinuations or deaths were observed in AMVUTTRA-treated patients.
- AMVUTTRA reduces serum vitamin A levels. Patients should take the recommended daily allowance of vitamin A, and tell their physician if they experience symptoms suggestive of vitamin A deficiency (e.g., night blindness).
- Efficacy results at 18 months were consistent with 9-month data, with AMVUTTRA achieving statistically significant improvements compared to external placebo for secondary endpoints including mNIS+7, Norfolk QoL-DN, 10-MWT and mBMI, and non-inferiority in serum TTR reduction relative to the within-study patisiran arm.⁷

Please see Important Safety Information and access full Prescribing Information for AMVUTTRA on the next page.

About RNAi Therapeutics

- RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today.⁸ This discovery was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.⁹
- By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function by silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing proteins, thus reducing their production.⁸

Access to AMVUTTRA: Alnylam Assist™

As part of Alnylam's commitment to making therapies available, Alnylam Assist™ offers a range of personalized patient support services to patients prescribed AMVUTTRA after a Start Form has been submitted, including helping patients understand their insurance coverage, financial assistance programs for eligible patients, educational materials to help facilitate conversations with doctors and family, and assistance with connecting to local resources. Patients will have access to Alnylam Case Managers and Alnylam Patient Education Liaisons throughout their treatment with AMVUTTRA. Physicians and patients can learn more about Alnylam's patient support program by visiting AlnylamAssist.com/AMVUTTRA for more information.

IMPORTANT SAFETY INFORMATION

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA™ treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with AMVUTTRA were arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

For additional information about AMVUTTRA, please see the full [Prescribing Information](#).

Endnotes

¹ Hanna M. *Curr Heart Fail Rep*. 2014;11:50-57.

² Mohty D, Damy T, Pierre C, et al. *Arch Cardiovasc Dis*. 2013;106:528-540.

³ Adams D, Coelho T, Obici L, et al. *Neurology*. 2015;85:675-682.

⁴ Maurer M, Bokhari S, Damy T, et al. *Circ Heart Fail*. 2019;12(9):e006075.

⁵ Nair JK, Attarwala H, Seghal A, et al. *Nucleic Acids Res*. 2017;45(19):10969-10977.

⁶ Adams D, et al. HELIOS-A: 9-month Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy. Presented at: 2021 American Academy of Neurology (AAN) Annual Meeting; April 17-22, 2021.

⁷ Adams D, et al. HELIOS-A: Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy. Presented at: 2022 American Academy of Neurology (AAN) Annual Meeting; April 2-7, 2022; Seattle, WA.

⁸ Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K, Tuschl T. *Nature*. 2001;411:494-8.

⁹ Zamore P. *Cell*. 2006;127:1083-1086.