

LETTER OF MEDICAL NECESSITY

**Use of AMVUTTRA® (vutrisiran) for
the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis**

To the HCP: The following is a sample letter of medical necessity template that can be customized based on your patient’s medical history and demographic information using your independent clinical judgment. You are responsible for providing information that completely and accurately represents your patient’s circumstances. Please note that some payers may have specific forms that must be completed in order to request prior authorization or to document medical necessity. Use of this document does not guarantee coverage or reimbursement by any third-party payer.

[Date]	RE: [Patient Name]
[Medical Director Name]	[Group Number]
[Payer Name]	[Policy Number]
[Payer Address Line 1]	[Claim Number]
[Payer City, State, ZIP]	[Diagnosis, ICD-10]

Dear [Medical Director],

I am writing this letter of medical necessity to request that my patient, [insert patient name], receive AMVUTTRA, a product that has been approved by the United States Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.¹

I. Hereditary Transthyretin-mediated (hATTR) Amyloidosis Disease Overview

hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, autosomal-dominant, multisystem, rapidly progressive, and fatal disease that manifests in adulthood. The condition is caused by variants in the transthyretin (TTR) gene that lead to destabilization of the tetrameric TTR protein. Subsequent misfolding and accumulation of TTR as amyloid deposits in various tissues throughout the body lead to heterogeneous clinical presentations, with multi-system dysfunction, including intractable polyneuropathy (e.g., sensorimotor neuropathy with pain and motor weakness and/or autonomic neuropathy such as diarrhea, orthostatic intolerance, sexual dysfunction) and cardiomyopathy, causing significant morbidity and mortality.^{2,3} Disease progression eventually leads to motor weakness, decreased pain sensation, generalized weakness, inability to perform activities of daily living, cachexia, loss of ambulation, and a progressive decline in physical functioning.^{4,5}

[Physician Footer]

Organs and tissues impacted include the nerves, heart, and gastrointestinal (GI) tract. Therefore, patients with this hereditary disease experience a spectrum of clinical manifestations. hATTR amyloidosis is a progressive, fatal disease, with a median survival of 4.7 years from diagnosis.^{4,6}

II. Product Description

AMVUTTRA® contains vutrisiran, a small interfering ribonucleic acid (siRNA) linked to a ligand that contains three N-acetylgalactosamine residues.¹ Vutrisiran causes the degradation of variant and wild-type TTR messenger RNA (mRNA) through RNA interference, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues.¹ Support for the efficacy and safety of AMVUTTRA consists of data from the treatment of adults with hATTR amyloidosis with polyneuropathy in a Phase 3, randomized, open-label trial (HELIOS-A: NCT03759379).

III. Rationale for Treatment

[Add additional information that is pertinent to your patient]

Based on the clinical safety and efficacy data of AMVUTTRA, it is my medical opinion that initiating treatment with AMVUTTRA for [patient's name] is appropriate and medically necessary at this time. Coverage of AMVUTTRA therapy, including all administration services (described in further detail below), should be reimbursed. The remainder of the letter describes the patient's medical history, prognosis, and rationale for treatment with AMVUTTRA.

Summary of Patient's Medical History

[Please complete based on your patient's medical history; delete any categories that are not pertinent to your patient]

- Date of hATTR amyloidosis diagnosis: [complete]
 - Diagnostic genetic testing: [If applicable, provide results of your patient's genetic testing including their genotype]
 - Other diagnostic evaluations: [e.g., bone scintigraphy scans, biopsy, abnormal test findings; please describe]
 - Other clinical signs: [If applicable, please describe]
- Family history of hATTR amyloidosis:
 - [Provide a brief description of relevant family history (e.g., affected family members, known outcomes)]
- Current signs and/or symptoms of the polyneuropathy of hATTR amyloidosis:
 - Peripheral sensorimotor polyneuropathy symptoms: [please describe]
 - Autonomic neuropathy symptoms: [e.g., orthostatic intolerance, gastrointestinal symptoms; please describe]
 - Other clinical signs of neuropathy: [e.g., sudomotor function test; please describe]

□ Previous/current treatments:

- [Describe previous and current treatment strategies (include treatments for polyneuropathy manifestations[e.g., for pain, gastrointestinal symptoms]); include the dose, start date, end date (if applicable) of each treatment, and reason for discontinuation (if applicable)]

IV. Dosing and Administration

Dosing and administration of AMVUTTRA® (vutrisiran) should be in accordance with U.S. Prescribing Information.¹ AMVUTTRA should be administered by a healthcare professional. The recommended dosage of AMVUTTRA is 25 mg administered via subcutaneous (SC) injection once every 3 months. See Section 2.2 of the U.S. Prescribing Information for complete administration instructions.¹

V. AMVUTTRA Efficacy and Safety Summary

HELIOS-A was a phase 3, randomized, open-label, multicenter, global study that was designed to evaluate the efficacy and safety of AMVUTTRA over 18 months, with a primary efficacy analysis conducted at Month 9, in adult patients presenting with a range of disease severities, genetic variants, and polyneuropathy symptoms caused by hATTR amyloidosis.⁷ The HELIOS-A study had three arms: an AMVUTTRA treatment arm, a patisiran treatment arm, and an external placebo control arm from the APOLLO* study.⁷ For the two active treatment arms, patients were randomized 3:1 to receive AMVUTTRA 25 mg by subcutaneous (SC) injection every 3 months (Q3M) or patisiran 0.3 mg/kg by intravenous (IV) infusion every 3 weeks (Q3W) for 18 months. The patisiran group was included in the study as a reference arm to help validate the comparison of AMVUTTRA vs. the external placebo control arm from APOLLO for the primary and secondary efficacy analyses. Baseline characteristics were comparable across treatment groups in HELIOS-A and APOLLO placebo groups.⁷

Polyneuropathy and Quality of Life

At month 9, the least squares (LS) mean change from baseline in the primary endpoint, modified Neuropathy Impairment Score plus 7 (mNIS+7) (used to measure neurologic impairment where a negative change from baseline indicates overall improvement), was significantly more favorable for the AMVUTTRA arm compared with the external placebo arm, with a treatment difference of -17.0 ($p < 0.001$).⁷ At Month 18, the AMVUTTRA group showed a statistically significant improvement in neuropathy, as measured by change from baseline in the mNIS+7 (least squares [LS] mean change from baseline: -0.46 points) versus the placebo group which showed a worsening of neuropathy (LS mean change from baseline: +28.1 points), with a treatment difference of 28.6 points (LS mean; $p < 0.001$).⁷ The treatment effect favoring AMVUTTRA at Months 9 and 18 was consistent across all components of mNIS+7 assessing the sensorimotor and autonomic aspects of the polyneuropathy. Furthermore, 48% of patients treated with AMVUTTRA showed an improvement in their mNIS+7 scores compared to baseline

*The APOLLO study was a Phase 3 randomized, double-blind, placebo-controlled study of patisiran that was conducted in adult patients with the polyneuropathy of hATTR amyloidosis comparable to the population studied in HELIOS-A.⁷

at 18 months, suggesting reversal of neuropathy impairment, compared with 4% of patients in the APOLLO placebo arm.⁷

The key secondary endpoint was Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN), which measures quality of life across domains relating to small fiber, large fiber, and autonomic nerve function, symptoms of polyneuropathy, and activities of daily living.⁹ A statistically significant improvement was observed for patients treated with AMVUTTRA® (vutrisiran) compared to placebo at month 9 and month 18 (p<0.001).⁷ The AMVUTTRA group showed continued improvement in quality of life through month 18, while the placebo group showed a worsening in quality of life. The majority of patients, 57%, treated with AMVUTTRA showed an improvement in the Norfolk QoL-DN relative to baseline at month 18 compared with 10% in the placebo group.⁷

The benefits of AMVUTTRA on mNIS+7 and Norfolk QoL-DN were consistent across all patient subgroups including age, sex, race, region, baseline NIS score, V30M genotype status, previous TTR stabilizer use, and disease stage.⁸

Ambulatory Ability, Activities of Daily Living, and Nutritional Status

Additional secondary endpoints in HELIOS-A were: the 10-meter walk test (10-MWT), which assesses gait speed as a measure of ambulatory ability; Rasch-built Overall Disability Scale (R-ODS), which evaluates patient-reported ability to perform activities of daily living such as eating, bathing, dressing, and standing; the modified body mass index (mBMI), which is a measure of nutritional status. All secondary endpoints were found to have a statistically significant improvement for patients treated with AMVUTTRA compared to placebo (p<0.001 for all measures).⁷

Table 1: HELIOS-A: Efficacy Results⁷

HELIOS-A Efficacy Endpoints	External Placebo IV Q3W (N=77) LS mean ± SE†	AMVUTTRA 25 mg SC Q3M (N=122) LS mean ± SE†	AMVUTTRA – Placebo LS mean difference† (95% CI)	p-value
Month 9 Primary Efficacy Analysis				
mNIS+7 ^{*,a}	14.76±2.00	-2.24±1.43	-17.00 (-21.78, -12.22)	p<0.001
Norfolk QOL-DN ^a	12.9±2.2	-3.3±1.7	-16.2 (-21.7, -10.8)	p<0.001
10-MWT (m/s) ^b	-0.133±0.025	-0.001±0.019	0.131 (0.070, 0.193)	p<0.001
Month 18 Efficacy Analysis				
mNIS+7 ^a	28.09±2.28	-0.46±1.60	-28.55 (-34.00, -23.10)	p<0.001
Norfolk QOL-DN ^a	19.8±2.6	-1.2±1.8	-21.0 (-27.1, -14.9)	p<0.001
10-MWT (m/s) ^b	-0.264±0.036	-0.024±0.025	0.239 (0.154, 0.325)	p<0.001
mBMI ^b	-115.7±13.4	25.0±9.5	140.7 (108.4, 172.9)	p<0.001
R-ODS ^b	-9.9±0.8	-1.5±0.6	8.4 (6.5, 10.4)	p<0.001

10-MWT=10-meter walk test; CI=confidence interval; IV=intravenous; LS=least squares; m/s, meters/second; mNIS+7=modified Neuropathy Impairment Score+7; Norfolk QOL-DN=Norfolk Quality of Life–Diabetic Neuropathy; Q3W=every 3 weeks; Q3M=every 3 months; SE=standard error; SC=subcutaneous

*primary endpoint, †change from baseline, ^adecrease (negative change) indicates improvement, ^bincrease (positive change) indicates improvement

Serum TTR Level

Patients in the AMVUTTRA arm achieved a rapid and sustained reduction in serum TTR levels (used to measure the pharmacodynamic effect of the drug) similar to patients in the patisiran reference arm. TTR

reduction with AMVUTTRA® (vutrisiran) was non-inferior to that observed with the within-study patisiran reference arm (secondary endpoint) over 18 months. The mean steady-state serum TTR reduction from baseline over 18 months was 88% for AMVUTTRA-treated patients.⁷

Safety Profile

In the HELIOS-A study, the majority of reported adverse events (AEs) were mild or moderate in severity.⁷ The most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).¹

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.¹

Closing Remarks

[Please provide closing comments relative to this patient's case (e.g., given the patient's existing signs and symptoms, the rapidly progressive nature of polyneuropathy of hATTR amyloidosis, and the demonstrated efficacy and safety of AMVUTTRA in treating polyneuropathy of hATTR amyloidosis, it is medically necessary and appropriate to initiate AMVUTTRA.]

Please contact my office at [insert phone number] if more information is needed. I look forward to receiving your timely response to this claim.

Sincerely,

[Insert physician name and provider number]

[Attachments: describe]

References:

1. AMVUTTRA Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
2. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
3. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29(Suppl 1):S14-26.
4. Conceição I, González-Duarte A, Obici L, et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;215:5-9.
5. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol*. 2021;268(6):2109-2122.
6. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid*. 2015;22(2):123-131.
7. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26.
8. Supplement to: Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26.
9. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2014;19(2):104-114.