SAMPLE LETTER OF MEDICAL NECESSITY TEMPLATE

**Use of AMVUTTRA® (vutrisiran) for patients with hereditary transthyretin-mediated (hATTR) amyloidosis who have cardiomyopathy concurrent with polyneuropathy (mixed-phenotype disease)**

**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® (vutrisiran), a product that is approved by the United States Food and Drug Administration (FDA) for treatment of 1) the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations and urgent heart failure visits, and 2) the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults.1

Based on the clinical safety and efficacy data of AMVUTTRA, it is my medical opinion that initiating treatment with AMVUTTRA is appropriate and medically necessary at this time. The costs of AMVUTTRA therapy, including all administration services, should be reimbursed. The remainder of this 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]***

**Diagnosis of hATTR Amyloidosis with Mixed Cardiac and Polyneuropathy Phenotype**

□ Genetic testing and/or family history of hereditary transthyretin-mediated (hATTR) amyloidosis:

* Genetic testing: [Please provide results of your patient’s genetic testing including their genotype]
* Family history: [If applicable, provide a brief description of relevant family history (e.g., affected family members, known outcomes)]

□ Date and method(s) of diagnosis of cardiac manifestations of hATTR amyloidosis:

* Date of diagnosis of cardiac manifestations of hATTR amyloidosis: [Date]
* Assessments of TTR amyloid deposition: [e.g., bone scintigraphy scans, cardiac scintigraphy scans, biopsy, mass spectrometry]
* Other diagnostic evaluations: [If applicable - e.g., other abnormal test findings indicative of cardiomyopathy of ATTR amyloidosis; please describe]
* Other clinical signs: [If applicable, please describe]

□ Date and method(s) of diagnosis of polyneuropathy manifestations of hATTR amyloidosis:

* Date of diagnosis of polyneuropathy manifestations of hATTR amyloidosis: [Date]
* Diagnostic evaluations: [e.g., abnormal test findings indicative of polyneuropathy of hATTR amyloidosis, bone scintigraphy scans, biopsy; please describe]
* Other clinical signs: [If applicable, please describe]

**Current Signs and/or Symptoms of Cardiomyopathy of ATTR Amyloidosis**

□ Patient has signs or symptoms consistent with the cardiomyopathy of ATTR amyloidosis:

* Cardiac signs / symptoms: [e.g., dyspnea, fatigue, edema, increased ventricular or atrial wall thickness, other hypertrophic features on echocardiography, intolerance to antihypertensive or heart failure medications due to symptomatic hypotension or orthostasis, discrepancy between LV wall thickness on imaging and QRS voltage on electrocardiogram, atrial fibrillation, AV block or prior pacemaker implantation, persistent mild increases in troponin levels, marked ECV expansion on CMR; please describe]
* Non-cardiac signs / symptoms:[e.g., bilateral carpal tunnel syndrome, lumbar spinal stenosis, hip or knee arthroplasty, history of biceps tendon rupture; please describe]

□ Disease stage: *[New York Heart Association (NYHA) Functional Class* ***OR*** *Gillmore Stage* ***OR*** *Columbia Stage; please describe]*

**Current Signs and/or Symptoms of the Polyneuropathy of hATTR Amyloidosis**

□ Patient has signs or symptoms consistent with the polyneuropathy of hATTR amyloidosis:

* Sensory-motor polyneuropathy symptoms: [please describe]
* Autonomic neuropathy symptoms: [e.g., orthostatic intolerance, diarrhea, constipation, delayed gastric emptying; please describe]
* Other clinical signs of neuropathy: [e.g., sudomotor function test; please describe]

**Previous/Current Treatments**

□ Previous and/or current treatment: [Describe previous and current treatment strategies (include treatments for cardiomyopathy manifestations [*e.g., dyspnea, fatigue, edema, etc.*] and/or polyneuropathy manifestations [*e.g., orthostatic intolerance, gastrointestinal symptoms, etc.*]); include the dose, start date, end date (if applicable) of each treatment, and reason for discontinuation (if applicable)]

**Prognosis**

□ Summary of professional opinion of the patient’s likely prognosis or potential disease progression without treatment with AMVUTTRA® (vutrisiran): [please describe]

**I. ATTR Amyloidosis Disease Overview**

ATTR amyloidosis is a progressive, debilitating, and ultimately fatal disease caused by misfolded transthyretin (TTR) protein.2 In ATTR amyloidosis, misfolded TTR accumulates as amyloid deposits in multiple tissues including the nerves, heart, and gastrointestinal (GI) tract, with corresponding clinical manifestations.2-4 Because TTR-derived amyloid deposits may accumulate throughout the body, a range of clinical manifestations is possible in ATTR amyloidosis, with some patients experiencing manifestations that are limited to a single organ system and some experiencing multisystemic manifestations.2,5-8

In hATTR amyloidosis with polyneuropathy (hATTR-PN), variants in the TTR gene 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 heterogenous 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), causing significant morbidity and mortality.9,10 Progression of polyneuropathy 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.5,11

Many patients with hATTR-PN also exhibit cardiomyopathy in association with hATTR amyloidosis (hATTR-CM). The co-occurrence of polyneuropathy and cardiomyopathy in patients with hATTR amyloidosis is referred to as “mixed-phenotype” disease, reflecting the multisystem clinical manifestation of this disease resulting from amyloid deposition throughout different tissues and organs in the body. In a manner that parallels TTR amyloid deposition in the nerves to cause the polyneuropathy manifestations of the disease, TTR-derived amyloid deposition in the myocardium causes the cardiomyopathy component of mixed-phenotype disease. Specifically, myocardial deposition of TTR amyloid causes the myocardial tissue to stiffen and the ventricular walls to thicken in a manner that prevents normal physiological functioning of the heart. This results in progressive cardiomyopathy and heart failure with multiple associated signs and symptoms.12,13

Aside from having progressive, debilitating consequences associated with the neuropathic and cardiac manifestations of the disease, mixed-phenotype hATTR amyloidosis is ultimately fatal, as both hATTR-CM and hATTR-PN are associated with premature mortality. In particular, available data demonstrate that hATTR is associated with a median survival of 4.7 years from diagnosis (the estimate of 4.7 years is from a population that included patients with polyneuropathy, patients with cardiomyopathy, and patients with mixed phenotype), while hATTR-CM is associated with a median survival duration of 2.6 to 5.8 years.14-19

**II. AMVUTTRA Efficacy and Safety in the Phase 3 HELIOS-A Trial (hATTR-PN)**

HELIOS-A was a global, open-label, phase 3 study evaluating the efficacy and safety of AMVUTTRA (vutrisiran) in adults with polyneuropathy due to hATTR amyloidosis.20 Patients were randomized 3:1 to receive vutrisiran 25 mg SC every 3 months or patisiran 0.3 mg/kg IV every 3 weeks for 18 months. Efficacy was assessed at Month 9 (including primary endpoint analysis) and Month 18, with comparisons made to an external placebo group from the APOLLO study (a randomized controlled study of patisiran in hATTR-PN) for clinical efficacy endpoints.20 The patisiran arm in HELIOS-A served as a common benchmark to validate population comparability between HELIOS-A and APOLLO, and it also served as an active comparator for vutrisiran on pharmacodynamic endpoints in HELIOS-A.

Baseline characteristics were similar across groups (HELIOS-A vutrisiran, APOLLO placebo, and HELIOS-A patisiran).20 At Month 9, vutrisiran provided a significant benefit on mNIS+7 (a measure of neurologic impairment, on which negative change indicates improvement), with a −17.0 point treatment difference vs. placebo (p<0.001). At Month 18, vutrisiran continued to show benefit (−28.6 points vs. placebo; p<0.001), with 48% of patients improving from baseline, compared with 4% in the placebo group.20

The key secondary endpoint, Norfolk QoL-DN, which measures neuropathy-related quality of life, also showed statistically significant benefit with vutrisiran over APOLLO placebo at both Month 9 and Month 18 (p<0.001). At Month 18, 57% of vutrisiran-treated patients showed improvement in Norfolk QoL-DN total score relative to their own pre-treatment baseline, vs. 10% on placebo.20

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.21

Vutrisiran also showed statistically significant benefit over APOLLO placebo (p<0.001) on all other secondary endpoints – including 10-MWT (gait speed), R-ODS (activities of daily living), and mBMI (nutritional status).20

Most adverse events were mild or moderate. The most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and reduced vitamin A (7%).1, 20

**III. AMVUTTRA Efficacy and Safety in the Phase 3 HELIOS-B Trial (ATTR-CM)**

Evidence for the efficacy and safety of AMVUTTRA for the treatment of ATTR-CM in adults was provided by HELIOS-B (N=654), a global, randomized, double-blind, placebo-controlled, phase 3 study in which 654 patients were equally randomized to receive vutrisiran 25 mg by SC injection Q3M or placebo for 33-36 months. Forty percent of the study population was receiving background treatment with the TTR stabilizer tafamidis at baseline in both the vutrisiran and placebo arms.21 The 654 patients randomized to receive vutrisiran or placebo made up the overall population in HELIOS-B. In addition to the overall HELIOS-B population, a separate monotherapy population (N=395; vutrisiran: n=196; placebo: n=199), comprising patients in the overall population who were not receiving tafamidis at baseline, was also defined. All primary and secondary endpoints were assessed in both the overall population and the monotherapy population.22

In the overall population of patients, treatment with vutrisiran resulted in a lower risk of the primary composite endpoint of death from any cause and recurrent cardiovascular events through up to 36 months compared with placebo (hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; P = 0.01) and a lower risk of the secondary endpoint of death from any cause through up to 42 months (hazard ratio, 0.65; 95% CI, 0.46 to 0.90; P = 0.01).22 In the monotherapy population, vutrisiran similarly reduced patients’ risk of the primary composite endpoint of death from any cause and recurrent cardiovascular events (hazard ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; P = 0.02) and their risk for the secondary endpoint of death from any cause through up to 42 months (hazard ratio, 0.66; 95% CI, 0.44 to 0.97; P = 0.045) relative to placebo.22 Vutrisiran also provided statistically significant and clinically meaningful benefit versus placebo across all other secondary endpoints, reflecting the preservation of physical capacity (as measured by 6-minute walk test) and patient-reported health-status and health-related quality of life (as measured by Kansas City Cardiomyopathy Questionnaire overall summary score) and the prevention of heart failure worsening (as measured by New York Heart Association heart failure class) in both the overall and the monotherapy population.22

Vutrisiran had an acceptable safety profile in HELIOS-B. The incidence of adverse events among patients in the vutrisiran group was similar to or lower than that among the patients in the placebo group, a finding that is consistent with the known profile of the drug. No new safety signs were identified. 22

**IV. Rationale for Treatment**

ATTR is a progressive disease. In the hereditary form of the disease, polyneuropathy is common, involving sensory-motor and autonomic nerve dysfunction, which result in lower limb numbness, pain, and gastrointestinal symptoms and ultimately lead to motor weakness, decreased pain sensation, generalized weakness, inability to perform activities of daily living, cachexia (weakness and wasting of the body due to severe chronic illness), a progressive decline in physical functioning, loss of ambulation, and eventually death.5,23,24 Patients with hATTR amyloidosis may also experience cardiomyopathy, which is marked by ongoing deterioration of heart function due to cardiac deposition of TTR amyloid, leading to declines over time in physical function and quality of life and subjecting patients to excess mortality risk. Many patients with hATTR amyloidosis exhibit a mixed phenotype of polyneuropathy and cardiomyopathy and are therefore subjected to the debilitating and life-threatening consequences of both of these aspects of the disease.25-27

Progression of polyneuropathy and cardiomyopathy, leading to the loss of physical function and quality of life, is observed in the absence of treatment in patients with mixed-phenotype hATTR amyloidosis. In addition, as hATTR amyloidosis progresses, management of the disease becomes increasingly difficult, and patients are increasingly subjected to excess mortality risk. This is especially concerning given the potentially irreversible nature of disease progression.19

AMVUTTRA, a silencer which reduces TTR production at the source, should be considered as an appropriate treatment in patients with hATTR amyloidosis presenting with mixed phenotype. AMVUTTRA demonstrated robust efficacy in hATTR-PN and ATTR-CM by meeting all prespecified primary and secondary endpoints in both the HELIOS-A and HELIOS-B trials, reflecting benefits with respect to stabilization or improvement of polyneuropathy (HELIOS-A), CV event risk and mortality reduction (HELIOS-B), quality of life, and physical function. In HELIOS-A, the most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity, arthralgia, dyspnea, and vitamin A decreased. In the HELIOS-B study, no new safety signals were identified.1,28 Based on the results of HELIOS-A and HELIOS-B, AMVUTTRA is the only therapeutic approved by the FDA to treat both hATTR-PN and ATTR-CM, allowing use as a single medication to treat both neuropathic and cardiac manifestations in mixed-phenotype hATTR amyloidosis. The available data therefore strongly support AMVUTTRA as a treatment for mixed-phenotype hATTR amyloidosis.

**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 ATTR amyloidosis, and the efficacy and safety profile of AMVUTTRA, it is medically necessary and appropriate to initiate AMVUTTRA therapy using the FDA-approved dosing regimen.]*

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: AMVUTTRA USPI (optional), and etc.]

**References**

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