LETTER OF MEDICAL NECESSITY

**Use of ONPATTRO® (patisiran) 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 ONPATTRO (patisiran), a product that is 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

1. **Hereditary Transthyretin-mediated (hATTR) Amyloidosis Disease Overview**

hATTR amyloidosis, also known as ATTRv amyloidosis, is a rare, autosomal-dominant, multisystem, rapidly progressive, and often 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 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) 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

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.5,6

1. **Product Description**

ONPATTRO® contains patisiran, a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, reducing serum TTR protein levels and TTR protein deposition in tissues.1 Support for the efficacy and safety of ONPATTRO consists of data from the treatment of adults with hATTR amyloidosis with polyneuropathy in a Phase 3 randomized, placebo-controlled trial (APOLLO: NCT01960348) and an long-term open-label extension study (Global OLE: NCT02510261).7,8

1. **Rationale for Treatment**

***[Add additional information that is pertinent to your patient]***

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

***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)]
1. **Dosing and Administration**

Dosing and administration of ONPATTRO® (patisiran) should be in accordance with U.S. Prescribing Information.1 ONPATTRO should be administered by a healthcare professional. ONPATTRO is administered via intravenous (IV) infusion. Dosing is based on actual body weight.1 My patient weighs [insert weight in kilograms], therefore, [he/she] should receive a dose of [insert dose] mg every three weeks. *[Please note, patients weighing ≥100 kg are recommended to receive a 30 mg dose per the U.S. Prescribing Information]*. To reduce the risk of an infusion-related reaction (IRR), the patient should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion.

1. **ONPATTRO Efficacy and Safety Summary**

The efficacy and safety of ONPATTRO were studied in the pivotal Phase 3, randomized, double-blind, placebo-controlled study, APOLLO, in patients with hATTR amyloidosis with polyneuropathy. Efficacy measures included a comprehensive set of endpoints assessing the impact of ONPATTRO on a broad range of polyneuropathy manifestations of hATTR amyloidosis.1,7 Results from the primary and secondary endpoints of the APOLLO study and the corresponding systems assessed by each endpoint are described below. All patients who completed APOLLO were eligible to be screened for enrollment into the 5-year Global OLE study.

***Polyneuropathy***

At 18 months in APOLLO, comparisons of the least squares (LS) mean change from baseline of the primary endpoint, modified Neuropathy Impairment Score plus 7 (mNIS+7), showed a 34.0 point improvement in patients treated with ONPATTRO vs placebo (p<0.001).1 Improvement was observed across all components of mNIS+7 assessing the sensorimotor and autonomic aspects of polyneuropathy.7 Furthermore, the majority of patients treated with ONPATTRO showed an improvement in their mNIS+7 scores compared to baseline suggesting reversal of neuropathy impairment.7 The secondary endpoint, Neuropathy Impairment Score-weakness (NIS-W), demonstrated statistically significant improvement in muscle weakness with ONPATTRO vs. placebo at 18 months (p<0.001).7

The Global OLE study showed that patients originally treated with ONPATTRO in APOLLO continued to demonstrate reversal of polyneuropathy from their APOLLO baseline, as measured by mNIS+7, through an additional 36 months of treatment. Additionally, patients originally treated with placebo in APOLLO had a halting of further polyneuropathy progression following 36 months of treatment with ONPATTRO in the Global OLE study. However, the 18-month treatment delay in this group resulted in accumulation of greater overall disease burden compared to patients who received ONPATTRO 18 months earlier in the APOLLO study.8

***Quality of Life and Activities of Daily Living***

The Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire, which includes domains relating to small fiber, large fiber, and autonomic nerve function, symptoms of polyneuropathy, and activities of daily living, was found to have a statistically significant difference in favor of ONPATTRO® (patisiran) vs. placebo at 18 months in APOLLO (p<0.001).1 The majority of patients treated with ONPATTRO showed an improvement in the Norfolk QOL-DN relative to baseline.6 The secondary endpoint of Rasch-Built Overall Disability Scale (R-ODS) score, which evaluates patient-reported ability to perform activities of daily living such as eating, bathing, dressing, and standing, and the measure of 10-meter walk test (10-MWT), which assesses gait speed, were both found to have a statistically significant difference in favor of ONPATTRO compared with placebo (p<0.001 for both measures).1,7

The Global OLE study showed that patients originally treated with ONPATTRO in APOLLO had a sustained and durable improvement in QOL, as measured by Norfolk QOL-DN, compared to their APOLLO baseline following an additional 36 months of treatment. Additionally, patients originally treated with placebo in APOLLO had an improvement in QOL following 36 months of treatment with ONPATTRO in the Global OLE study.8

***Autonomic Neuropathy Manifestations and Nutritional Status***

The secondary endpoint Composite Autonomic System Symptom Score (COMPASS-31), which measures patient-reported autonomic neuropathy symptoms such as dizziness, constipation, diarrhea, nausea/vomiting, and incontinence, and the modified body mass index (mBMI), which is a measure of nutritional status, both demonstrated statistically significant differences in favor of ONPATTRO compared with placebo at 18 months (p<0.001) in APOLLO.1

**Post-Orthotopic Liver Transplantation (OLT)**

An open-label study was done to evaluate safety and efficacy of patisiran in patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) with polyneuropathy progression post-orthotopic liver transplant. In the Post-OLT Study, the primary endpoint was the average of Month 6 and Month 12 percent reduction from baseline in serum transthyretin (TTR). Analysis of this endpoint showed that patients treated with ONPATTRO experienced a rapid and sustained reduction in serum TTR levels. Averaged across Months 6 and 12, the median percent reduction from baseline in serum TTR was 91.0% (95% CI: 86.1, 92.3; p<0.001).9

*Additional content to support use of patisiran in patients with prior liver transplant:*

[Analyses of secondary endpoints showed improvement in neuropathy, quality of life, and autonomic symptoms with ONPATTRO treatment, demonstrated by decreases from baseline to Month 12 in NIS score (mean [SEM] change from baseline of –3.7 [2.7]), Norfolk QOL-DN score (mean [SEM] change from baseline of –6.5 [4.9]), and COMPASS 31 score (LS mean [SEM] change from baseline of –5.0 [2.6]), respectively. Through 12 months of ONPATTRO treatment, measures of disability in activities of daily living and social participation (R-ODS score) and nutritional status (mBMI) appeared to be stable compared to baseline (mean [SEM] change from baseline of –0.1 [1.1] for R-ODS, and +4.4 [21.8] for mBMI).9 ]

***Safety Profile***

In the pivotal Phase 3 trial, APOLLO, the most frequently reported adverse reactions that occurred in at least 10% of ONPATTRO-treated patients and occurred at least 3% more frequently than in the placebo-treated patients were upper respiratory tract infections (29% vs 21%) and infusion-related reactions (19% vs 9%).1 The safety profile of ONPATTRO remains consistent with previous studies following an additional 36 months of ONPATTRO dosing in the Global OLE study and in the post-OLT study. ONPATTRO continues to show a positive benefit:risk profile.8-9

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO.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 hATTR amyloidosis, and the existing efficacy and safety of ONPATTRO, it is medically necessary and appropriate to initiate ONPATTRO 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: describe]

**References:**

1. ONPATTRO (patisiran) Prescribing Information [package insert]. 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. doi:10.1186/1750-1172-8-31
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. doi:10.1097/WCO.0000000000000289
4. 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. doi:10.1007/s00415-019-09688-0
5. Conceição I, González-Duarte A, Obici L, et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9. doi:10.1111/jns.12153
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. doi: 10.3109/13506129.2015.1019610
7. Adams D, Gonzalez-Duarte A, O’Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
8. Wixner J, Ueda M, Marques W Jr, et al. Patisiran Global Open-Label Extension Study at 36 Months: Effect of Long-Term Treatment on Mortality and Ambulatory Function in Patients with hATTR Amyloidosis with Polyneuropathy. XVIII International Symposium on Amyloidosis (ISA); September 4-8, 2022; Heidelberg, Germany.
9. Schmidt HH, Wixner J, Planté-Bordeneuve V, et al. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation*. Am J Transplant*. 2022;22(6):1646-1657. doi: 10.1111/ajt.17009