Sample Letter of Medical Necessity

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[Date]

[Name of Medical Director] [Title]
[Name of Insurer]
[Address of Insurer]
[City, State, Zip Code]

Re: [Patient's Name]
[Patient ID Number]
[Diagnosis code(s) and description(s)]

I am writing to provide additional information regarding the medical necessity of treating one of your members, **[Patient Name]**, with Tegsedi® (inotersen) injection for subcutaneous, self-administered use. TEGSEDI was approved by the FDA on October 5th, 2018 and is a transthyretin-directed antisense oligonucleotide (ASO) indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (PN-hATTR) in adults.[1] This letter provides a disease overview, information about my patient's medical history, and my rationale for use of TEGSEDI.

Disease Overview

Hereditary transthyretin amyloidosis (hATTR) is an under-recognized, debilitating and progressive disease.[2,3] The hereditary type of ATTR (hATTR) impacts multiple organ systems resulting in a number of potential complications that have a significant negative effect on quality of life.[4] Non-specific symptoms and clinical manifestations overlap with other common disorders which can result in delayed diagnosis.[5,6] In addition, many patients see multiple physicians prior to hATTR confirmation through genetic testing.[7,8] Hereditary ATTR amyloidosis is caused by a point mutation in the TTR gene leading to misfolding of the transthyretin (TTR) protein and subsequent protein aggregation and the formation of amyloid fibrils. Over 130 mutational variants of the TTR gene have been identified and are expressed in an autosomal dominant pattern with variable penetrance.[7,8] Hereditary ATTR amyloid with polyneuropathy is a highly debilitating and irreversible neurological disorder typically presenting with symptoms of progressive sensorimotor and autonomic neuropathy.[9]

Patient's Diagnosis and History

The history and course of PN-hATTR for **[Patient Name]** are as follows:

Diagnosis of PN-hATTR with E85.1 (Neuropathic heredofamilial amyloidosis)
Insert comment / information regarding the date and method of diagnosis:

- **MUST include comment on genetic confirmation of a pathogenic mutation associated with hATTR**
- **MAY include evidence of amyloid by biopsy of tissue such as from the salivary gland, subcutaneous fatty tissue of the abdominal wall or sural nerve**
- **SHOULD include clinical manifestations [e.g., working diagnosis prior to PN-hATTR confirmation such as neuropathy, nephropathy, ocular manifestations, bilateral carpal tunnel syndrome (CTS), lumbar spinal canal stenosis, etc.]**

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Signs, Symptoms, Scoring / Staging of Polyneuropathy
Insert clinical signs and symptoms of disease progression:

- **MUST include baseline Polyneuropathy Disability (PND) score and/or Familial Amyloidosis Polyneuropathy (FAP) stage**
- **MUST include clinical evidence of peripheral and/or autonomic neuropathy (e.g., symmetrical length-dependent peripheral neuropathy, orthostatic hypotension, sexual dysfunction, uncontrolled diarrhea, alternating diarrhea/constipation, etc.)**
- **SHOULD include impact on quality of life, activities of daily living or impact upon the caregiver**
- **SHOULD include comment on patient hospitalizations, and/or frequency of office visits**

Previous treatments: **[Insert comment / information on current therapy and previous treatments identified to manage or slow the progression of the disease and resulting symptoms, included but not limited to those related to CTS, spinal canal stenosis, GI symptoms, ocular manifestations, neuropathy, and renal failure.]**

Despite the use of a variety of therapies to treat the symptoms of PN-hATTR described in this letter, my patient continues to decline in daily function and their quality of life is significantly impacted by this disease. It is my opinion that TEGSEDI injection is appropriate therapy for my patient.

Treatment Description and Rationale

TEGSEDI is available in a single-dose, prefilled syringe with a safety spring (284 mg/1.5 mL solution, 27-gauge, 8-mm needle), providing patients with a once-weekly subcutaneous injection.[1] Patients have the ability to self-administer at a time and place that works for them.[1] TEGSEDI is available only through a restricted distribution program under a REMS due to the risk of thrombocytopenia and glomerulonephritis.[1] Patients must enroll in the program and comply with ongoing monitoring requirements.[1] TEGSEDI has a manageable safety profile.[1] Please see Important Safety Information that begins on page 3.

TEGSEDI prevents the synthesis of the TTR proteins in the liver through degradation of the TTR mRNA.[1] In the pivotal trial described below, initiation of TEGSEDI therapy substantially (median range: 75% to 79%) reduced TTR protein levels with the reduction sustained through 65 weeks.[1] This trial was a robust, randomized, double-blind, placebo-controlled, multicenter clinical trial in adults with polyneuropathy caused by PN-hATTR.[1] Patients were randomized in a 2:1 ratio to receive either TEGSEDI (n=113) or placebo (n=60), respectively as a subcutaneous injection administered once per week for 65 weeks.[1] The coprimary efficacy end points were the change from baseline to week 66 in the modified Neuropathy Impairment Score + 7 (mNIS+7) and Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) scores.[1]

TEGSEDI significantly improved measures of neuropathy vs placebo.[1] Patients treated with TEGSEDI achieved a 19.7-point benefit at 66 weeks vs patients receiving placebo (P<0.001).[1] More than 1/3 of patients treated with TEGSEDI saw improvements in neuropathy at 66 weeks (37% vs 19%) vs patients receiving placebo, P=0.033).[10]

TEGSEDI significantly improved quality of life vs placebo.[1] Patients treated with TEGSEDI achieved a clinically meaningful 11.7-point benefit in Norfolk QoL-DN total score at 66 weeks vs patients receiving placebo (P<0.001).[1] Nearly half of patients treated with TEGSEDI saw improvements in quality of life at 66 weeks (49% vs 23% on placebo, P=0.003).[1] For the mNIS+7 and Norfolk QoL-DN measures, patients treated with TEGSEDI experienced similar improvements regardless age, sex, race, region, Neuropathy Impairment Score (NIS), Val30Met mutation status, and disease stage.[1]

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In the NEURO-TTR open-label extension (OLE) study, extended dosing with TEGSEDI demonstrated continued slowing in neuropathy progression after 2 years of follow-up compared to the natural history of the disease. TEGSEDI was not associated with additional safety concerns or increased toxicity. The longest any patient has been on inotersen was 5.2 years (data through May 31, 2018).[11]

Given the seriousness of my patient's condition and the aforementioned reasons, it is my professional medical opinion that **[Patient Name]** should receive treatment with TEGSEDI.

I certify that both the patient and the health provider understand the requirements of and are in compliance with the parameters of the TEGSEDI Risk Evaluation and Mitigation Strategy (REMS) program.

Print Name: _____ Signature: _____ Date: _____

I trust that this information is helpful to you in understanding why I have prescribed treatment with TEGSEDI. If you require any additional information, please do not hesitate to contact me at **[(XXX) XXX-XXXX]**.

Sincerely,

[Physician's Name MD]
[Title and/or Name of Practice]
[Address]
[City, State, Zip Code]
[Phone]
[Email]

Enclosures: **[Clinic notes, Prescribing Information, FDA approval letter, other supportive medical literature]**

INDICATION

TEGSEDI is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

IMPORTANT SAFETY INFORMATION

WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

<u>Thrombocytopenia</u>

- **TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. One clinical trial patient died from intracranial hemorrhage**
- **TEGSEDI is contraindicated in patients with a platelet count below 100 x 10^9/L**
- **Prior to starting TEGSEDI, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75 x 10^9/L or greater, and more frequently if values are less than 75 x 10^9/L**

- **If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible. The patient should not receive additional TEGSEDI unless a platelet count is determined to be interpretable and acceptable by a medical professional**
- **Following discontinuation of treatment for any reason, continue to monitor platelet count for 8 weeks, or longer if platelet counts are less than normal, to verify that platelet counts remain above 75 x 10^9/L**

Glomerulonephritis

- **TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. One clinical trial patient who developed glomerulonephritis and did not receive immunosuppressive treatment remained dialysis-dependent. In clinical trials, cases of glomerulonephritis were accompanied by nephrotic syndrome, which can have manifestations of edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection**
- **TEGSEDI should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher**
- **Prior to starting TEGSEDI, measure the serum creatinine, estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPCR), and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every 2 weeks. TEGSEDI should not be given to patients who develop a UPCR of 1000 mg/g or higher or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause**
- **If a dose is held, once eGFR increases to ≥45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued**

TEGSEDI REMS Program

- **Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, TEGSEDI is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program**

CONTRAINDICATIONS

TEGSEDI is contraindicated in patients with

- Platelet count below 100 x 10^9/L
- History of acute glomerulonephritis caused by TEGSEDI
- History of a hypersensitivity reaction to TEGSEDI

WARNINGS AND PRECAUTIONS

Thrombocytopenia

TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia that can be life-threatening. In Study 1, platelet counts below 100 x 10^9/L occurred in 25% of TEGSEDI-treated patients compared with 2% of patients on placebo. Platelet counts below 75 x 10^9/L occurred in 14% of TEGSEDI-treated patients compared with no patients on placebo. One patient in a clinical trial experienced a fatal

intracranial hemorrhage. Do not initiate TEGSEDI in patients with a platelet count below 100 x 10^9/L. Follow recommended monitoring and treatment recommendations for platelet count.

Symptoms of thrombocytopenia can include unusual or prolonged bleeding (eg, petechiae, easy bruising, hematoma, subconjunctival bleeding, gingival bleeding, epistaxis, hemoptysis, irregular or heavier than normal menstrual bleeding, hematemesis, hematuria, hematochezia, melena), neck stiffness, or atypical severe headache. Patients and caregivers should be instructed to be vigilant for symptoms of thrombocytopenia and seek immediate medical help if they have concerns.

Glomerulonephritis and Renal Toxicity
TEGSEDI can cause glomerulonephritis that may result in dialysis-dependent renal failure. In Study 1, glomerulonephritis occurred in 3 (3%) TEGSEDI-treated patients compared with no patients on placebo. One patient did not receive immunosuppressive treatment and remained dialysis-dependent. If glomerulonephritis is suspected, pursue prompt diagnosis and initiate immunosuppressive treatment as soon as possible. Follow recommended monitoring and treatment recommendations for renal parameters. TEGSEDI should generally not be initiated in patients with a UPCR of 1000 mg/g or greater. If acute glomerulonephritis is confirmed, TEGSEDI should be permanently discontinued.

TEGSEDI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TEGSEDI REMS Program because of risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis.

Stroke and Cervicocephalic Arterial Dissection
TEGSEDI may cause stroke and cervicocephalic arterial dissection. In clinical studies, 1 of 161 (0.6%) TEGSEDI-treated patients experienced carotid artery dissection and stroke. Educate patients on the symptoms of stroke and central nervous system arterial dissection. Instruct patients to seek help as soon as possible if symptoms of stroke or arterial dissection occur.

Inflammatory and Immune Effects
Inflammatory and immune changes are an effect of some antisense oligonucleotide drugs, including TEGSEDI. In clinical studies, serious inflammatory and immune adverse reactions occurred in TEGSEDI-treated patients, including immune thrombocytopenia and glomerulonephritis, as well as a single case of antineutrophil cytoplasmic autoantibody (ANCA)–positive systemic vasculitis.

Liver Injury
In clinical studies, 8% of TEGSEDI-treated patients had an increased alanine aminotransferase (ALT) at least 3 times the upper limit of normal (ULN) compared with 3% of patients on placebo; 3% of TEGSEDI-treated patients had an ALT at least 8 times the ULN compared with no patients on placebo. Monitor ALT, aspartate aminotransferase, and total bilirubin at baseline and every 4 months during treatment with TEGSEDI. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with TEGSEDI, as appropriate.

Liver Transplant Rejection

In a clinical study, cases of liver transplant rejection were reported 2-4 months after starting TEGSEDI in patients whose liver allografts had previously been clinically stable (for over 10 years) prior to starting TEGSEDI. In these cases, the patients clinically improved and transaminase levels normalized after glucocorticoid administration and cessation of TEGSEDI.

In patients with a history of liver transplant, monitor ALT, AST, and total bilirubin monthly. Discontinue TEGSEDI in patients who develop signs of liver transplant rejection.

Hypersensitivity Reactions/Antibody Formation
TEGSEDI can cause hypersensitivity reactions. In clinical studies, 6 of 161 (4%) TEGSEDI-treated patients stopped treatment because of a hypersensitivity reaction. These reactions generally occurred within 2 hours of administration of TEGSEDI. Antibodies to TEGSEDI were present when the reactions occurred. If a hypersensitivity reaction occurs, discontinue administration of TEGSEDI and initiate appropriate therapy. Do not use in patients who have a history of hypersensitivity reactions to TEGSEDI.

Uninterpretable Platelet Counts: Reaction Between Antiplatelet Antibodies and Ethylenediaminetetraacetic acid (EDTA)
In Study 1, 23% of TEGSEDI-treated patients had at least 1 uninterpretable platelet count caused by platelet clumping compared with 13% of patients on placebo. If there is suspicion of EDTA-mediated platelet clumping, perform a repeat platelet count using a different anticoagulant (eg, sodium citrate, heparin) in the blood collection tube. Recheck the platelet count as soon as possible if a platelet measurement is uninterpretable. Hold TEGSEDI dosing until an acceptable platelet count is confirmed with an interpretable blood sample.

Reduced Serum Vitamin A Levels and Recommended Supplementation
TEGSEDI treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking TEGSEDI. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (eg, night blindness).

ADVERSE REACTIONS

The most common adverse reactions that occurred in at least 20% of TEGSEDI-treated patients and more frequently than in those on placebo were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever. Serious adverse reactions were more frequent in TEGSEDI-treated patients (32%) than in patients on placebo (21%).

DRUG INTERACTIONS

Because of the risk of thrombocytopenia, caution should be used when using antiplatelet drugs (including nonprescription products that affect platelets) or anticoagulants concomitantly with TEGSEDI. Because of the risk of glomerulonephritis and renal toxicity, caution should be used when using nephrotoxic drugs and other drugs that may impair renal function concomitantly with TEGSEDI.

Please see full Prescribing Information, including boxed WARNING, at TEGSEDIhcp.com.

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[1] TEGSEDI [package insert]. Boston, MA: Akcea Therapeutics, Inc; 2019.
[2] Adams D, Amitay O, Coelho T. Patients with hereditary ATTR amyloidosis experience an increasing burden of illness as the disease progresses. Orphanet J Rare Dis. 2015;10(suppl 1):P58.
[3] 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.
[4] Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *Am J Manag Care*. 2017;23(suppl 7):S107-S112.
[5] Lousada I, et al. Orphanet J Rare Dis. 2017;12(suppl 1):165.
[6] Lousada I, et al. Presented at: the First European Congress on Hereditary ATTR Amyloidosis. November 2015; Paris, France
[7] Gertz MA, et al. Advances in the treatment of hereditary transthyretin amyloidosis: A Review. *Brain and Behavior*. 2019;00:e01371. https://doi.org/10.1002/brb3.1371
[8] Hou X, Aguilar MI, Small DH. FEBS J. 2007;274(7):1637-50.
[9] Adams D, Suhr OB, Hund E, et al; European Network for TTR-FAP (ATTReuNET). First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy.
[10] Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis [supplemental appendix]. *N Engl J Med*. 2018;379(1):1-36. doi:10.1056/NEJMoa1716793.
[11] Gertz M ASH 2018 Oral Presentation Long-Term Update from the OLE of the NEURO-TTR Study

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