

## New Drug Evaluations: Drugs for Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis

**Date of Review:** July 2019

**Generic Name:** patisiran

**Generic Name:** inotersen

**Brand Name (Manufacturer):** Onpattro™ (Alnylam Pharmaceuticals Inc.)

**Brand Name (Manufacturer):** Tegsedi™ (Ionis Pharmaceuticals, Inc.)

### **Purpose for Class Update:**

To evaluate the evidence for efficacy and safety of patisiran and inotersen in the treatment of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (hATTR).

### **Research Questions:**

1. Is patisiran safe and effective in improving clinically meaningful outcomes, including improvements in disease progression, quality of life, and survival in patients with hATTR?
2. Is inotersen safe and effective in improving clinically meaningful outcomes, including improvements in disease progression, quality of life, and survival in patients with hATTR?
3. Are there subgroups of patients with hATTR for which patisiran or inotersen is more effective or associated with fewer adverse events?

### **Conclusions:**

- There is low quality evidence, based on one randomized controlled trial with high risk of bias, that patisiran may improve neurologic impairment in polyneuropathy of hATTR, demonstrated by a statistically significant reduction in the modified neurologic impairment score (mNIS + 7) compared to placebo (-6 points versus +28 points; mean difference -34 points; 95% Confidence Interval [CI] -39.9 to -28.1).<sup>1</sup> However, it remains unknown if this difference in the mNIS + 7 is clinically relevant or noticeable to the patient since this outcome has not been validated or used in other clinical trials.
- There is low quality evidence that patisiran modestly improves quality of life compared to placebo in patients with polyneuropathy of hATTR, as measured by the Norfolk-Quality of Life-Diabetic Neuropathy Scale (Norfolk-QoL-DN) (-6.7 vs. 14.4; least squares [LS] mean difference -21.1; 95% CI -27.2 to -15.0).<sup>1</sup> This scale has been validated for use in patients with Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP), but there is not a defined minimum clinically important difference.
- There is insufficient evidence that patisiran decreases cardiovascular outcomes or improves survival and does not improve disease progression or ambulation compared to placebo.
- There did not appear to be an increase in serious adverse events, death or discontinuations due to adverse events with patisiran compared to placebo. However, long term safety of patisiran, which is the first in its class, is unknown due to insufficient data.
- There is low quality evidence, based on one randomized controlled trial with high risk of bias, that inotersen slows the progression of neurologic impairment compared to placebo, measured by the change in mNIS+7 score from baseline (+5.8 points vs. +25.5 points; treatment different -19.7; 95% CI -26.4 to -13)

and stabilizes quality of life, measured by the Norfolk-QoL-DN (1 point vs. 12.7 points; treatment difference -11.7; 95% CI -18.3 to -5.1).<sup>2</sup> The clinical significance associated with these changes is unknown.

- There is insufficient evidence that inotersen decreases cardiovascular outcomes or improves survival and does not improve disease progression.
- There are significant safety concerns associated with inotersen, including severe thrombocytopenia, potentially irreversible glomerulonephritis, hepatic accumulation, and neurotoxicity. Based on only one small clinical trial, the magnitude of harm remains unknown at this time.
- It is difficult to generalize results of available studies to the United States (U.S.) population with a low number of U.S. participants included in trials. Very few patients with the most common hATTR genotype in the U.S. (Val122Ile) were included in clinical trials for patisiran (0.9%) and inotersen (1.7%)

#### **Recommendations:**

- Create Preferred Drug List (PDL) class for Drugs for hATTR.
- Designate inotersen and patisiran as non-preferred medications.
- Implement clinical prior authorization criteria for patisiran and inotersen to ensure appropriate utilization (**Appendix 2**).

#### **Background:**

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant disorder caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver that normally functions as a transporter of thyroxine and retinol (vitamin A).<sup>3</sup> The disorder presents in a spectrum of clinical presentations due to amyloid deposits, including a predominantly neurologic phenotype (familial amyloid polyneuropathy [FAP]) and a predominantly cardiac phenotype (familial cardiomyopathy [FAC]). However, hATTR can present with both cardiac and neurologic manifestations. There are over 120 TTR reported mutations. Some mutations are more strongly associated with polyneuropathy (V30M) and some with cardiomyopathy.<sup>4</sup> The most common mutation in the U.S. is the V122I mutation, which typically leads to cardiomyopathy.<sup>5</sup> The second most common mutation in the U.S. is T60A, which causes a mixed neuropathy and cardiomyopathy presentation.<sup>5</sup> Deterioration in activities of daily living and ambulation are seen due to neuropathic changes as well as autonomic dysfunction. Additionally, hATTR can affect multiple organ systems resulting in weight loss, wasting, difficulty walking, and alternating constipation and diarrhea, often due to autonomic nerve involvement. Cardiac manifestations can include heart failure, arrhythmias, orthostatic hypotension or sudden death due to severe conduction disorders. Survival of 5 to 15 years is expected after the onset of FAP and only 2 to 5 years for those with cardiomyopathy. The exact incidence is unknown but is estimated to be 1/100,000 in U.S. Caucasians.<sup>6</sup> The estimated worldwide prevalence of FAP is 5,000 to 10,000 with approximately 100 to 2500 individuals in the US.<sup>6</sup> Symptoms of FAP typically appear between 30 and 55 years of age. Death is commonly a result of cardiac dysfunction, infection or cachexia.<sup>6</sup>

Standard of care for hATTR has been limited to liver transplantation and administration of transthyretin tetramer stabilizers.<sup>7</sup> Liver transplant has been the treatment of choice for those with neuropathy but no cardiac involvement. Transplantation is most effective when initiated early in the course of the disease in those with V30M mutations. Other treatment options for hATTR-associated polyneuropathy include tafamidis and diflunisal; however, neither medication was FDA approved in the U.S. for FAP until recently. Diflunisal, a non-steroidal anti-inflammatory (NSAID), is used off-label in the U.S, but long-term use is limited due to risks associated with NSAIDs, including gastrointestinal bleeding, renal insufficiency and cardiovascular events. More recently, tafamidis was FDA approved for the cardiomyopathy phenotype and will be reviewed at a future meeting. Both drugs have been shown to slow progression of neurologic impairment to a small extent.

The goal of treatment is to stabilize disease progression and potentially reverse neuropathy, as well as improve quality of life. There is no established test or study outcome that has been found to be adequate in quantifying disease severity and overall symptom burden of hATTR. The Neurologic Impairment Scale

[NIS] +7 , the primary study outcome in clinical trials, was modified from scales used in tafamidis and diflunisal trials to better reflect overall symptoms and impairment of hATTR.<sup>4</sup> These are described in more detail below; however, it remains difficult to quantify a meaningful change in these complex outcomes and how it relates to disease progression and overall perceived benefit to the patient. Additionally, these complicated and time-consuming assessments are subject to variability between investigators and extensive training is required.

RNA interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering ribonucleic acids. Newer agents, including patisiran, are RNAi agents that reduce the production of transthyretin by targeting the untranslated region of transthyretin mRNA in the liver.<sup>6</sup> Patisiran was the first agent approved for treatment of hATTR and was granted breakthrough designation by the FDA in 2018 after initial denial in 2013 due to discussion of the modified primary outcomes.<sup>6</sup> Patisiran is approved for polyneuropathy associated with hATTR and is administered intravenously (IV) every three weeks. Inotersen is an antisense oligonucleotide that binds TTR messenger RNA and induces its degradation. It is administered as a once weekly subcutaneous injection.<sup>8</sup> Both of these agents are only approved for the FAP phenotype of hATTR.

#### **Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

#### **Systematic Reviews:**

None identified

#### **New Guidelines:**

There were no clinical guidelines identified that include either patisiran or inotersen.

#### **NEW DRUG EVALUATION:** Patisiran (Onpattro™)

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

#### **Clinical Efficacy:**

Patisiran was FDA approved for polyneuropathy of hATTR based on one phase 3, randomized, double-blind, placebo-controlled trial evaluating patisiran IV every 21 days compared to matched placebo for 18 months.<sup>1</sup> Subjects in the trial were required to have a NIS of 5 to 130. The NIS ranges from 0 to 244, with higher scores indicating more impairment. The inclusion range was carefully selected to include patients with disease advanced enough to have progression in the placebo group, but not so advanced to mask a treatment effect.<sup>4</sup> Subjects also had to have a polyneuropathy disability (PND) score of IIIb or lower and adequate

liver and renal function. The PND score is a five-stage measure of neuropathy impairment ranging from 0 (no impairment) from 4 (confined to wheelchair or bedridden). Full inclusion and exclusion criteria can be found in the evidence table (**Table 4**).

There was a statistically significant difference in baseline TTR genotype with 52% of patients in the placebo group having the V30M genotype and only 38% of patients in the patisiran group.<sup>1</sup> This is the most common genotype that is associated with early onset disease and has the highest response rates to liver transplantations. However, this genotype is less prevalent in the U.S. Additionally, the mean baseline NIS score was 3.5 points higher in the patisiran group, indicating more severe impairment, compared to the placebo group. Lastly, patients in the patisiran group had more cardiac manifestations (61%) compared to placebo (47%). These baseline differences increase the risk of bias and could reflect differences in disease severity at baseline and impact the ability to compare the two groups. Additional limitations that contribute to an increased risk of bias include an unequal attrition rate in the patisiran group (7%) versus placebo (29%) and possible unblinding due to infusion related reactions.<sup>1</sup> More patients in the placebo group discontinued study drug due to adverse events (9% vs. 2%) and due to disease progression (5% vs. < 1%) compared to patisiran. However, nearly half of discontinuations were unexplained and it is not clear why many placebo patients discontinued study treatment.

The primary outcome was change from baseline in the modified neurologic impairment score (mNIS+7) at 18 months.<sup>1</sup> Response to treatment was defined as a less than 10-point increase from baseline. This includes a clinical exam-based exam of neurologic impairment combined with electrophysiologic measures of small and large nerve fiber function and measurement of autonomic function (postural blood pressure). The mNIS+7 used in this trial was modified from the original NIS+7 to better assess total body sensation, autonomic function, and nerve conduction.<sup>4</sup> This is a very complex 304 point assessment tool that includes multiple scoring components (presented in **Table 1**) and required training of neuromuscular physicians.<sup>4</sup> While an increase in total score indicates worsening impairment, it is unclear how to evaluate changes in the score and what constitutes a clinically meaningful improvement. Additionally, this score was modified and has not been validated or used in previous clinical trials. Older neuropathy impairment assessment tools do have defined minimal clinically important differences but were determined to be unsuccessful in reflecting neuropathic symptoms from hATTR.<sup>3</sup> The FDA clinical reviewer noted that many of the individual components of the score (nerve conduction) are biomarkers that do not, by themselves, represent direct clinical benefit.<sup>6</sup> Additionally, differences in other components of the score (motor and sensory function by neurologic exam) detected by the physician might not be noticeable to the patient or result in improved function in daily activities.<sup>6</sup> The FDA reviewer suggested results would need to be evaluated in context of results secondary endpoints.

A secondary outcome was quality of life, measured by the Norfolk-Quality of Life-Diabetic Neuropathy Scale (Norfolk-QoL-DN). This is a 35- item patient-reported measure that evaluates patients' perception of impairment and was originally developed to assess patients' perceptions of symptoms associated with diabetic neuropathy.<sup>10</sup> It has a maximum possible score of 136, with higher scores indicating greater impairment, or worse quality of life. This scale has been validated for use in patients with TTR-FAP, but there is not a defined minimum clinically important difference.<sup>10</sup>

**Table 1: Modified Neurologic Impairment Scores Used as Primary Outcomes in Trials of Patisiran and Inotersen**

	<b>APOLLO Trial (Patisiran)</b>	<b>NEURO-TTR (Inotersen)</b>
<b>Total Score</b>	304	346.3
<b>Assessment (Score)</b>		
<b>Motor strength/weakness</b>	Neurologic exam (192)	Neurologic exam (192)
<b>Reflexes</b>	Neurologic exam (20)	Neurologic exam (20)
<b>Sensation</b>	Quantitative sensory testing (80)	Quantitative sensory testing (80) + additional sensations (32)

<b>Composite nerve conduction score</b>	Σ5 – ulnar compound muscle action potential (CMAP) and sensory nerve action potential (SNAP), peroneal CMAP, tibial CMAP, sural SNAP (10)	-18.6 points to 18.6 points
<b>Autonomic function</b>	Postural blood pressure (2)	Heart rate response to deep breathing (-3.72 points to 3.72 points)

Overall, there was a statistically significant change from baseline in the mNIS+7 with patisiran compared to placebo (-6.0 vs. 28; LS mean difference, -34.0 points; 95% CI -39.9 to 28.1), indicating a potential improvement in neurological function in the patisiran group and a worsening in the placebo group.<sup>1</sup> The clinical significance of a change in 6 points is unclear. However, the FDA notes that this observed improvement is not consistent with the natural history of the disease.<sup>6</sup> The effect was largely driven by muscle strength and quantitative sensory testing (QST). Strength testing could also be affected by changes in motivation by the subject or provider. However, QST is unlikely to be affected by motivation. Significantly more patients in the patisiran group experienced neurologic improvement compared to placebo (56% vs. 4%; ARR 52%; NNT 2), defined as a decrease in mNIS+7.

There was also a statistically significant difference in quality of life, measured by change from baseline in Norfolk-QoL-DN, in the patisiran group compared to placebo (-6.7 vs. 14.4; LS mean difference -21.1; 95% CI -27.2 to -15.0).<sup>1</sup> Patients on patisiran showed modest improvements in physical function/large fiber neuropathy, symptoms and autonomic domains while placebo patients reported worsening in all five domains.

There were statistically significant differences in all secondary polyneuropathy outcomes including: disability (Rasch-built Overall disability scale), gait speed (10-meter walk test), nutritional status (modified-body mass index), and an assessment score of autonomic symptoms (COMPASS 31), consistent with the positive findings of the primary outcome.<sup>1</sup> These were all measured by scales with unclear minimum clinical differences. The difference in gait speed from the 10-MWT was 0.311 meters per second.<sup>1</sup> Disease progression was measured by the polyneuropathy disability score (PND) and FAP stage. FAP stage remained stable in 76% of patisiran patients and only 5 (3%) of patients reported improved FAP stage.<sup>9</sup> No placebo patient reported improved FAP stage, but the groups were not statistically compared. Additionally, ambulation (PND score) only improved in 12 (8%) of patisiran patients and 0 of the placebo patients.<sup>9</sup> There is insufficient evidence to make conclusions on the effect of patisiran on cardiovascular outcomes in patients with cardiovascular manifestations.

Only 20% of patients were from the U.S., which has a different genotype mix than other countries, limiting generalizability to the U.S. population. There were very few patients with the most common genotype found in the U.S. (Val122Ile). This trial was not designed to demonstrate patients improved on treatment and FDA approval was largely based on the idea that any improvement from baseline is inconsistent with the natural history of the disease.<sup>6</sup> Long-term benefits and effects on survival are unclear.

#### **Clinical Safety:**

The most common adverse events associated with patisiran were upper respiratory infections and infusion reactions (**Table 2**). Discontinuations due to adverse events were more common in the placebo group than patisiran. There were four serious adverse events of atrioventricular block in the patisiran group. There did not appear to be a difference in overall deaths between the two groups (5% vs. 8%) and all deaths in the patisiran group were due to cardiovascular causes. This could be due to the natural history of the disease; but the causes of deaths in the placebo group were variable.

**Table 2: Adverse Reactions Occurring in at least 5% of Patisiran-treated Patients and More Frequently Than Placebo**

	<b>Patisiran</b>	<b>Placebo</b>
<b>Peripheral edema</b>	30%	22%
<b>Upper respiratory tract infections</b>	29%	21%
<b>Infusion related reaction</b>	19%	9%
<b>Dyspepsia</b>	8%	4%
<b>Muscle spasms</b>	8%	1%
<b>Arthralgia</b>	7%	0
<b>Dyspnea</b>	7%	0
<b>Erythema</b>	7%	3%
<b>Bronchitis</b>	7%	3%
<b>Vertigo</b>	5%	1%

**Table 3. Pharmacology and Pharmacokinetic Properties.**

<b>Parameter</b>	
Mechanism of Action	Patisiran is a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues
Oral Bioavailability	N/A - Administered intravenously
Distribution and Protein Binding	Distributed primarily in the liver. Protein binding is low (<2.1%)
Elimination	<1% excreted unchanged in urine
Half-Life	3 days
Metabolism	Metabolized by nucleases to shorter nucleotides.

Abbreviations: mRNA: messenger RNA; N/A: not applicable; siRNA: small interfering ribonucleic acid; TTR: transthyretin

**Comparative Endpoints:****Clinically Meaningful Endpoints:**

- 1) Quality of life
- 2) Functional Improvement
- 3) Disease Progression
- 4) Survival
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

**Primary Study Endpoint:**

- 1) Change from baseline in modified NIS+7 score at 18 months

**Table 4. Comparative Evidence Table.**

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. APOLLO <sup>1,4</sup> PC, MC, DB, RCT	1. Patisiran 0.3 mg/kg IV Q 21 days  2. Placebo (0.9% NACL)  All patients received the following pre-medications:  -Dexamethasone IV (10 mg) or equivalent, - Oral APAP 500 mg -Intravenous H2 blocker -intravenous H1 blocker (diphenhydramine 50 mg or equivalent)  Duration: 21 months	<b>Demographics:</b> Patients with hATTR polyneuropathy Mean mNIS+7 (80.9 patisiran, 74.6 placebo) Median age 62 74% male, stage 1 FAP 46.2%, Val30Met: 42.7%  <b>Key Inclusion Criteria:</b> Age 18-85, diagnosis of hATTR with peripheral neuropathy, NIS of 5 to 130, Karnofsky performance status* of ≥ 60%, ANC ≥ 1500, platelet ≥ 100,000, Hg ≥ 10 g/dl, AST/ALT < 2.5 x ULN, normal bilirubin, albumin ≥ 3 g/dl INR ≤ 1.2, Scr ≤ 1.5 x ULN, negative HBV and HCV, negative pregnancy test, 2 methods of contraception  <b>Key Exclusion Criteria:</b> Low vitamin A or B12 levels, liver transplant, type 1 diabetes or type 2 diabetes for ≥ 5 years, HIV, heart failure, recent ACS, unstable angina, anticipated survival < 2 years, use of TTR stabilizers (tafamidis, diflunisal)	<b>Randomized:</b> 148 77  <b>mITT:</b> 141 67  <b>PP:</b> 137 51  <b>Attrition:</b> 29 (38%) 11 (7%)	<b>Primary Endpoint:</b> Change from baseline in mNIS+7 (least squares mean change [SE])  1. -6.0±1.7 2. 28.0±2.6 Difference -34.0 points; (95% CI -39.9 to -28.1) P<0.001  <b>Improvement in mNIS+7</b> 1. 56% 2. 4% OR 39.9; (95% CI 11-144.4) P<0.01  <b>Secondary Endpoints:</b> Quality of life (change from baseline in Norfolk QOL-DN questionnaire)  1. -6.7±1.8 2. 14.4±2.7 LS mean difference -21.1 points; (95% CI -27.2 to -15) P<0.001  Improvement in Norfolk-QOL-DN:  1. 51.4% 2. 10.4% OR 10.0; ( 95% CI 4.4 to 22.5)	NA  ARR 52%; NNT 2  NA  ARR 41%; NNT 3	<b>D/C due to AE:</b> 1. 3 (2.0%) 2. 7 (9.1%)  <b>Death:</b> 1. 7 (4.7%) 2. 6 (7.8%)  <b>Infusion-related reaction:</b> 1. 28 (19%) 2. 7 (9%)  P values and 95% CI not reported	NA  NA  NA	<b>Risk of Bias (low/high/unclear):</b> <b>Selection Bias:</b> High; randomization via interactive response system; treatment concealed to all but unblinded personnel. However, significant differences in baseline characteristics between groups (TTR genotype, baseline NIS score, cardiac involvement, etc.) <b>Performance Bias:</b> Unclear; double-blinded to patient and provider, double-dummy design. However, possibility of unblinding due to infusion related reactions. <b>Detection Bias:</b> Low; Personnel blinded to lab results that could unblind treatment (vitamin A, thyroid tests, etc.) <b>Attrition Bias:</b> High; modified ITT population was only used for secondary and exploratory outcomes. The primary endpoint and first secondary endpoint were analyzed using the PP population and missing data were not imputed; high and unequal attrition in each group. Nearly half of discontinuations were unexplained. <b>Reporting Bias:</b> Low. All pre-specified outcomes reported <b>Other Bias:</b> high; Protocol and statistical analysis plan was developed by Alnylam Pharmaceuticals. Sponsor-employed authors were involved in analyzing the data and preparing the first draft. Editorial assistance was provided by Adelphi Communications, under contract with Alnylam Pharmaceuticals.  <b>Applicability:</b> <b>Patient:</b> Under representation of US patients and genotype most common in the US (VAL122Ile mutation). Extensive exclusion criteria also limits generalizability. <b>Intervention:</b> Patisiran IV Q 21 days. There are no data to evaluate a dose-response with respect to clinical efficacy. <b>Comparator:</b> Placebo as comparator. No appropriate active comparator based on lack of FDA approved treatments. <b>Outcomes:</b> Complex outcome measures used which are difficult to interpret. Lack of clinically meaningful outcomes. <b>Setting:</b> 46 sites across 19 countries (US, France, Taiwan, Spain, Japan, Germany, Mexico, Portugal, South Korea, Sweden, Bulgaria, Italy, Canada, Turkey, Cyprus, Brazil, Netherlands, UK, Argentina). 21% of patients in North America, but distribution uneven between groups (13% vs. 25%)

**Abbreviations** [alphabetical order]: ACS = acute coronary syndrome; AE =adverse effects; ANC = absolute neutrophil count; APAP = acetaminophen; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; D/C = discontinuation; FAP = familial amyloid polyneuropathy; ITT = intention to treat; H2 = histamine 2; hATTR = hereditary transthyretin-mediated amyloidosis; HBV = hepatitis B virus; HCV = hepatitis C virus; Hg = hemoglobin; HIV = human immunodeficiency virus; IV= intravenous; MC = multi-center; mITT = modified intention to treat; mNIS = modified neuropathic impairment score; N = number of subjects; NA = not applicable; NaCl = normal saline; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SE = standard error; TTR = transthyretin; ULN = upper limit of normal

\*Karnofsky performance status measures a patient's functional status and ranges from 0 to 100 (0=death and 100 = normal function)

## **NEW DRUG EVALUATION: Inotersen (Tegsedi™)**

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

### **Clinical Efficacy:**

Inotersen was FDA approved based on one phase 3, randomized, double-blind, placebo-controlled trial comparing inotersen 300 mg weekly subcutaneous injection to placebo for 15 months in patients hATTR patients with polyneuropathy.<sup>2</sup> Similar to the previous trial evaluating patisiran, patients had to have a baseline NIS of 10 to 130. Patients received three injections in the first week, followed by weekly injections and all patients received vitamin A supplementation. Fifty-two percent of patients had the Val30M TTR mutation and the majority of patients were still ambulatory (67%).<sup>2</sup>

The primary endpoints were the same as the patisiran trial (mNIS+7 and Norfolk-QOL-DN) and are described in detail above. However, the mNIS+7 was modified slightly differently in this trial compared to the patisiran trial (**Table 1**). A lower score represents better neurologic function, and there is insufficient data to suggest a minimum clinically important difference for either scale. The authors of the trial suggest a 2-point difference as being clinically significant.<sup>2</sup> However, the studies cited for this statement evaluated the original NIS and NIS+7 scales and are not applicable to the modified scale used in this study.

Differences in baseline characteristics (**Table 7**) increase the risk of bias. Patients in the inotersen group had more severe sensorimotor and autonomic neuropathy, a higher baseline mNIS + 7 (79.35 vs. 74.12), and a higher proportion of patients with cardiac symptoms compared to placebo (67% vs. 55%).<sup>8</sup> Additionally, discontinuation rates were relatively high and differed between inotersen (22.3%) and placebo (13.3%). Only 3 patients (1.7%) had the Val122Ile mutation, the most common genotype seen in the U.S.

There was a significant difference in the primary outcome, change in mNIS+7 from baseline, between inotersen and placebo (treatment difference -19.7; 95% CI -26.4 to -13).<sup>2</sup> Both groups experienced neuropathy progression from baseline, but the inotersen group experienced a reduced level of progression in mNIS +7 (5.8 points) compared to placebo (25.5 points).<sup>2</sup> More patients in the inotersen group experienced an improvement in mNIS+7 compared to placebo (36.5% vs. 19.2%).<sup>2</sup> Similarly, there was a statistically significant difference in quality of life scores between inotersen and placebo (treatment difference -11.7; 95% CI -18.3 to -5.1) and significantly more patients in the inotersen group reported improvement in quality of life compared to placebo (50% vs. 26.9%). Still, half of the patients receiving inotersen did not report any improvement. It is uncertain if these treatment differences correlate to a clinically meaningful improvement for patients.

There were no differences in disease progression, measured by the polyneuropathy disability score (PND), a five-stage measure of neuropathy impairment ranging from 0 (no impairment) to 4 (confined to a wheelchair or bedridden).<sup>9</sup> Although it was not compared statistically, more patients in the placebo group reported improvements or stabilization in the PND score (65% vs. 58%). Comparable proportions of patients in the two groups reported a worsening in disease stage. There was also no significant difference in modified body mass index.

**Clinical Safety:**

The most common side effects occurring in 10% or more of patients and twice as frequently as placebo are included in **Table 5**. There were more discontinuations due to adverse effects (13% vs. 2%) and more serious adverse events (32% vs. 22%) in the inotersen group compared to placebo, respectively.

There were 5 deaths in the inotersen group and zero in the placebo group. Four were considered related to disease progression and one possibly from the drug (intracranial hemorrhage associated with severe thrombocytopenia). Two significant safety concerns associated with inotersen include severe thrombocytopenia and glomerulonephritis. Decreased platelet count occurred in 54% of inotersen patients compared to 13% of placebo patients and platelet counts less than 100 X 10<sup>9</sup>/L occurred in 25% of inotersen patients, compared with 2% of placebo patients.<sup>8</sup> Glomerulonephritis occurred in 3 patients (3%) treated with inotersen and no patients on placebo. Additional safety concerns include liver toxicity, inflammatory and immune changes, and CNS toxicity (arterial dissection, stroke).<sup>8</sup> In these patients, stopping inotersen alone was not sufficient to correct glomerulonephritis. Additionally, seven patients stopped inotersen due to hypersensitivity reactions associated with antibody formation to inotersen. FDA review recommended post-marketing studies to further evaluate the risks of thrombocytopenia, glomerulonephritis and neurologic toxicity using a Risk Evaluation and Mitigation Strategies (REMS) program. Additional warnings and precautions are included in the drug label. Based on available data and long half-life of inotersen (32 days), the magnitude for serious harm remains unknown.

**Table 5: Adverse Events See in Inotersen Trial**

	<b>Inotersen (n=112)</b>	<b>Placebo (n=60)</b>
<b>Decreased Platelets</b>	54%	13%
<b>Nausea</b>	31%	12%
<b>Headache</b>	23%	12%
<b>Pyrexia</b>	20%	8%
<b>Vomiting</b>	15%	5%
<b>Anemia</b>	13%	3%
<b>Thrombocytopenia</b>	13%	2%

**Table 6. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Inotersen is an antisense oligonucleotide that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.
Oral Bioavailability	N/A; subcutaneous injection
Distribution and Protein Binding	Highly bound to plasma proteins (>94%); rapidly distributes to tissues, with the highest concentrations seen in the kidney and liver (volume of distribution 293 L)
Elimination	Cleared through metabolism; < 1% excreted unchanged in urine
Half-Life	32.3 days
Metabolism	Metabolized by nucleases to shorter nucleotides.

Abbreviations: mRNA: messenger RNA; TTR: transthyretin

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Quality of life
- 2) Functional Improvement
- 3) Survival
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change from baseline in modified NIS+7 score at week 66
- 2) Change in baseline in Norfolk QOL-DN at week 66



**Abbreviations** [alphabetical order]: ACS = acute coronary syndrome; ANC = absolute neutrophil count; APAP = acetaminophen; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; FAP = familial amyloid polyneuropathy; FAS = full analysis set; ITT = intention to treat; H2 = histamine 2; hATTR = hereditary transthyretin-mediated amyloidosis; Hg = hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTN = hypertension; LOCF = last observation carried forward; MC = multi-center; mITT = modified intention to treat; mNIS = modified neuropathic impairment score; N = number of subjects; NA = not applicable; NaCl = normal saline; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NYHA = New York heart association; OR = odds ratio; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SE = standard error; TTR = transthyretin; TSH = thyroid stimulating hormone; ULN = upper limit of normal

\*Karnofsky performance status measures a patient's functional status and ranges from 0 to 100 (0=death and 100 = normal function)

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONPATTRO™ safely and effectively. See full prescribing information for ONPATTRO.

**ONPATTRO (patisiran) lipid complex injection, for intravenous use**

**Initial U.S. Approval: 2018**

#### INDICATIONS AND USAGE

ONPATTRO contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

#### DOSAGE AND ADMINISTRATION

- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks by intravenous infusion. For patients weighing 100 kg or more, the recommended dosage is 30 mg (2.1)
- Premedicate with a corticosteroid, acetaminophen, and antihistamines (2.2)
- Filter and dilute prior to administration (2.3)
- Infuse over approximately 80 minutes (2.4)

#### DOSAGE FORMS AND STRENGTHS

Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial (3)

#### CONTRAINDICATIONS

None (4)

#### WARNINGS AND PRECAUTIONS

- Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs (5.1)
- Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur (5.2)

#### ADVERSE REACTIONS

The most frequently reported adverse reactions (that occurred in at least 10% of ONPATTRO-treated patients and at least 3% more frequently than on placebo) were upper respiratory tract infections and infusion-related reactions (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 8/2018**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TEGSEDI™ safely and effectively. See full prescribing information for TEGSEDI.

TEGSEDI (inotersen) injection, for subcutaneous use  
Initial U.S. Approval: 10/2018

### WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS

See full prescribing information for complete boxed warning.

#### Thrombocytopenia

- TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. (5.1)
- Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.1)

#### Glomerulonephritis

- TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. (5.2)
- Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.2)

TEGSEDI is available only through a restricted distribution program called the TEGSEDI REMS Program (5.3).

## INDICATIONS AND USAGE

TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults (1).

## DOSAGE AND ADMINISTRATION

- The recommended dosage is 284 mg administered by subcutaneous injection once weekly. (2.1)
- Laboratory tests must be measured prior to treatment, continue to be monitored after treatment initiation, and for 8 weeks following discontinuation of treatment, as directed. (2.3, 2.4)

## DOSAGE FORMS AND STRENGTHS

Injection: 284 mg/ 1.5 mL in a single-dose prefilled syringe (3)

## CONTRAINDICATIONS

- Platelet count less than  $100 \times 10^9/L$  (4, 5.1)
- History of acute glomerulonephritis caused by TEGSEDI (4, 5.2)
- Patients with a history of a hypersensitivity reaction to TEGSEDI (4, 5.7)

## WARNINGS AND PRECAUTIONS

- *Stroke and Cervicocephalic Arterial Dissection:* These adverse events occurred within 2 days of first dose and with symptoms of cytokine release. Educate patients on symptoms of stroke and central nervous system arterial dissection. (5.4)
- *Inflammatory and Immune Effects:* Serious neurologic adverse reactions consistent with inflammatory and immune effects occurred. (5.5)
- *Liver Effects:* Monitor alanine amino transferase, aspartate aminotransferase, and total bilirubin every 4 months during treatment and in case of symptoms of hepatic dysfunction. (5.6)
- *Hypersensitivity Reactions:* If these occur, discontinue and initiate appropriate therapy. (5.7)
- *Uninterpretable Platelet Counts: Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid:* Platelet clumping can cause uninterpretable platelet measurement; repeat test if this is suspected. (5.8)
- *Reduced Serum Vitamin A Levels and Recommended Supplementation:* Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. (5.9)

## ADVERSE REACTIONS

The most common adverse reactions (those that occurred in at least 20% of TEGSEDI-treated patients and more frequently than on placebo) were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals, Inc. at 1-833-642-5232 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

Appendix 2: Proposed Prior Authorization Criteria

**Drugs for Hereditary Transthyretin-Mediated Amyloidosis (hATTR)**

**Goal(s):**

- To limit utilization of medications for hATTR to FDA-approved indications.

**Length of Authorization:**

Up to 6 months

**Requires PA:** (Both pharmacy and physician-administered claims)

- All medications indicated for hATTR

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

**Table 1: FDA approved therapies for hATTR amyloidosis**

Drug	Indication
Inotersen	Polyneuropathy of hATTR
Patisiran	Polyneuropathy of hATTR
Tafamidis	Cardiomyopathy of hATTR

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is this an FDA approved indication of hATTR amyloidosis supported by transthyretin mutation proven by genetic testing (See Table 1)?	<b>Yes:</b> Go to #5 Document genotype.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have clinical signs and symptoms of disease (peripheral/autonomic neuropathy, motor disability)?	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6. Is the patient on Vitamin A supplementation?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
7. Is the request for or is the patient on concurrent use of more than one hATTR therapy (including diflunisal)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #8
8. Has the patient had a liver transplantation?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #9
9. Is baseline disease severity documented (Baseline polyneuropathy disability (PND) score and Familial amyloid polyneuropathy (FAP) stage)?	<b>Yes:</b> Document values. Go to #10	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
10. Was the medication prescribed or in consultation with a neurologist?	<b>Yes:</b> Go to #11	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
11. Is the request for patisiran?	<b>Yes:</b> Approve for 6 months	<b>No:</b> Go #12
12. Is the request for inotersen?	<b>Yes:</b> Go to # 13	<b>No:</b> Go to #15
13. Has a baseline platelet count been obtained in the previous 3 months and are $\geq 125 \times 10^9/L$ ?	<b>Yes:</b> Go to #14  Document baseline platelet count: _____ Date of Lab: _____	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
14. Has baseline renal function been evaluated in the previous 3 months?	<b>Yes:</b> Approve for 6 months  Document baseline serum creatinine and BUN: _____ Date of Lab: _____	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Approval Criteria		
15. Is the request for a newly approved hATTR therapy and does the indication match the FDA approved indication?	<b>Yes:</b> Approve for 6 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

  

Renewal Criteria		
1. Has the patient had a documented response to treatment including at least one of the following: a. Improved neurologic impairment b. Improved motor function c. Improved quality of life	<b>Yes:</b> Go to #2	<b>No:</b> Pass to RPh; Deny (medical appropriateness)
2. Has the patient experienced stabilization OR improvement from baseline in one of the following: a. Baseline polyneuropathy disability (PND) score b. Familial amyloid polyneuropathy (FAP) stage	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh; Deny (medical appropriateness)
3. Is the renewal for inotersen?	<b>Yes:</b> Go to #4	<b>No:</b> Approve for 12 months
4. Does the patient have a platelet count $\geq 100 \times 10^9/L$ ?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 7/19 (MH)  
Implementation: 8/19/19