**FDA APPROVED INDICATIONS AND DOSAGE**¹, ⁵, ⁶

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage</th>
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</thead>
<tbody>
<tr>
<td><strong>Onpattro™</strong> (patisiran)</td>
<td>The treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults</td>
<td>For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg once every 3 weeks For patients weighing 100 kg or more, the recommended dosage is 30 mg once every 3 weeks Dosing is based on actual body weight</td>
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<tr>
<td>Intravenous infusion</td>
<td></td>
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<tr>
<td><strong>Tegsedi™</strong> (inotersen)</td>
<td>The treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults</td>
<td>284 mg subcutaneous injection once weekly</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
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</tbody>
</table>

**CLINICAL RATIONALE**

Hereditary transthyretin-mediated (hATTR) amyloidosis in adults is a rapidly progressive, life threatening disease caused by mutant transthyretin (TTR) proteins that form amyloid deposits in tissues throughout the body. The TTR circulating in the body is primarily produced by the liver. Accumulation of these amyloids leads to progressive multisystem dysfunction, including polyneuropathy and cardiomyopathy. The peripheral and autonomic nerve systems are the most commonly affected tissue. Sensory peripheral neuropathy, pain and temperature sensation are the most severely affected. Motor impairments occur later in the disease progression, causing wasting and weakness. The impairment of the autonomic nervous system may include dyshidrosis, sexual impotence, alternating diarrhea and constipation, orthostatic hypotension, and urinary incontinence. In some cases, the main clinical manifestation is carpal tunnel syndrome, while ocular impairment can also occur.¹ Diagnosis can be confirmed via biopsy of the affected tissue followed by staining with Congo red. Genetic testing is also a crucial component to confirm a hATTR amyloidosis diagnosis as it identifies the specific TTR mutation present.², ¹⁰

Staging the disease is based on degree of ambulation. Patients are scored using the FAP (Familial Amyloid Polyneuropathy) scale. Stage 0 patients are asymptomatic, but have the variant TTR gene and amyloid deposits. Stage 1 patients are ambulatory, stage 2 are ambulatory with assistance, and stage 3 patients are bedridden or wheelchair bound. Pharmacologic treatment is reserved for stage 1 and 2 patients.⁷ The polyneuropathy disability score (PND) is also of used for these patients. Patients are scored on their
ambulation. A score of I indicates preserved walking and sensory disturbances. A PND of II indicates impaired walking, but can ambulate without a stick or crutch. PND IIIa is walking with 1 stick or crutch, while PND IIIb necessitates 2 sticks or crutches. PND IV patients are confined to a wheelchair or are bedridden. Another test, the modified Neuropathy Impairment Score +7 (mNIS+7) is a more comprehensive test in assessing topographical sensation. It has emerged as the primary outcome measure in studies concerning hATTR patients.

**Efficacy**

Patisiran is a double-stranded small interfering ribonucleic acid (siRNA) formulated as a lipid nanoparticle complex for delivery to hepatocytes. Patisiran causes the 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. The APOLLO trial randomized 225 patients with hereditary transthyretin amyloidosis withpolyneuropathy, in a 2:1 ratio, to receive IV patisiran (0.3 mg/kg) (148 patients) or placebo (77 patients) once every 3 weeks. The primary endpoint was the change in baseline on the modified Neuropathy Impairment Score+7 (mNIS+7), while other assessments were the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, 10-meter walk test, and modified body-mass index times albumin lever as a marker of nutritional status.

At 18 months, the least squares mean change for mNIS+7 was -6.0±1.7 in the treatment group versus 28.0±2.6 in the placebo group (-34.0 points, p<0.001). The change in Norfolk QOL-DN was -6.7±1.8 versus 14.4±2.7 (-21.1 points, p<0.001). Gait speed in the 10-meter walk test was increased (0.08±0.02 m/s vs -0.24±0.04 m/s, difference 0.31 m/s, p<0.001), as was a decrease in the lowering of the BMI (-3.7±9.6 versus -119.4±14.5, 115.7 difference, p<0.001). Patisiran has been shown to stabilize or improve a patient’s PND and FAP scores through an exploratory endpoint in the APOLLO trial.

Inotersen is a modified antisense oligonucleotide that inhibits the hepatic production of transthyretin protein. Inotersen binds to TTR, leading to the degradation of TTR by RNase. The NEURO-TTR trial randomized 172 hereditary transthyretin amyloidosis withpolyneuropathy patients in a 2:1 ratio to receive 300mg of inotersen (112) or placebo (60). Primary endpoints were the change in the mNIS+7 score and the change in the Norfolk QOL-DN score. At 66 weeks, both primary efficacy assessments favored inotersen. The least squares mean change from baseline was -19.7 points (95% CI, -26.4 to -13.0; p<0.001) for the mNIS and -11.7 points (95% CI, -18.3 to -5.1; P<0.001) for the Norfolk QOL-DN score. Improvements were independent of disease stage, mutation type, or presence of cardiomyopathy.

**References**

hATTR Amyloidosis Neuropathy Prior Authorization with Quantity Limit

TARGET AGENTS

Onpattro™ (patisiran)

Tegsedi™ (inotersen)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onpattro (patisiran)</td>
<td>62706060102020</td>
<td>M, N, O, or Y</td>
<td>30 mg (comes in 5ml vials, 30mg=3 vials=15ml)/ 21 days</td>
</tr>
<tr>
<td>Tegsedi (inotersen)</td>
<td>6270104010E520</td>
<td>M, N, O, or Y</td>
<td>6ml (4 syringes)/ 28 days</td>
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</table>

CRITERIA FOR APPROVAL

Initial Evaluation

Target Agents will be approved when ALL of the following are met:

1. ONE of the following:
   a. The patient has a confirmatory diagnosis of hATTR amyloidosis by mutation of the TTR gene with polyneuropathy confirmed by genetic testing or by biopsy OR
   b. The patient has another FDA approved indication for the requested agent and route of administration AND

2. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND

3. The patient does NOT have any FDA labeled contraindications to the requested agent AND

4. ONE of the following:
   a. The requested dose does not exceed the program quantity limit OR
   b. ALL of the following:
      i. The requested dose is greater than the program quantity limit AND
      ii. The requested dose does not exceed the maximum FDA labeled dose for the requested indication AND
      iii. The requested dose cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

Renewal Evaluation

Target Agents will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis
   AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
5. ONE of the following:
   A. The requested dose does not exceed the program quantity limit OR
   B. ALL of the following:
      i. The requested dose is greater than the program quantity limit
         AND
      ii. The requested dose does not exceed the maximum FDA labeled dose for the requested indication
         AND
      iii. The requested dose cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

**Length of Approval:** 12 months