Introduction

Amyloid is an abnormal protein. There are many different reasons why the body makes amyloid. One cause is a change to the TTR gene. This gene provides instructions to the liver about how to make a ceratin protein. But changes to the TTR gene means this liver protein is faulty. These faulty liver proteins get deposited throughout the body and build up over time. This condition is known as hereditary transthyretin-mediated amyloidosis (hATTR). Symptoms like numbness, pain and weakness in the arms and legs, heart problems, and stomach and bowel problems develop as the condition progresses. One way to treat hATTR is to use certain drugs to reduce the amount of TTR protein the liver makes. This policy describes when these types of drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
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</table>
| Onpattro™ (patisiran) | **Onpattro™ may be considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis when:**  <br>• Patient is 18 years of age or older  <br>AND  <br>• Documented transthyretin (TTR) mutation verified by genetic testing  <br>AND  <br>• Presence of symptoms consistent with polyneuropathy of hereditary transthyretin amyloidosis  <br>  o Peripheral sensorimotor polyneuropathy (eg, tingling or increased pain in the hands or feet, loss of feeling or numbness in the hands or feet, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking)  <br>OR  <br>  o Autonomic neuropathy (eg, postural hypotension, sexual dysfunction, recurrent urinary tract infection)  <br>AND  <br>• Polyneuropathy disability (PND) score IIIb or less or familial amyloid polyneuropathy (FAP) stage 2 or less  <br>AND  <br>• Not used in combination with the following: TTR stabilizers (eg, tafamidis, diflunisal) and Tegsedi™ (inotersen)  <br>AND  <br>• Prescribed by or in consultation with a neurologist  <br>AND  <br>• Dose is based on actual body weight as follows:  <br>  o For patients weighing less than 100 kg, the dosage is 0.3 mg/kg once every 3 weeks  <br>  o For patients weighing 100 kg or more, the dosage is 30 mg once every 3 weeks  <br>  <br>Note:  <br>• Clinical description of PND score  <br>  • Score 0 = No symptoms  <br>  • Score 1 = Sensory disturbances but preserved walking capability
**Drug** | **Medical Necessity**
---|---
- | -
- | -
- | -
- | -
- | -
- | -
| Score II = Impaired walking capacity but ability to walk without a stick or crutches | -
| Score IIIA = Walking with the help of one stick or crutch | -
| Score IIIB = Walking with the help of two sticks or crutches | -
| Score IV = Confined to a wheelchair or bedridden | -

**Note:** Clinical description of FAP stage
- Stage 0 = No symptoms
- Stage 1 = Unimpaired ambulation
- Stage 2 = Assistance with ambulation required
- Stage 3 = Wheelchair-bound or bedridden

**Tegsedi™ (inotersen)**

**Tegsedi™ may be considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis when:**
- Patient is 18 years of age or older
  - **AND**
  - Documented transthyretin (TTR) mutation verified by genetic testing
  - **AND**
  - Presence of symptoms consistent with polyneuropathy of hereditary transthyretin amyloidosis
    - Peripheral sensorimotor polyneuropathy (eg, tingling or increased pain in the hands or feet, loss of feeling or numbness in the hands or feet, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking)
      - **OR**
        - Autonomic neuropathy (eg, postural hypotension, sexual dysfunction, recurrent urinary tract infection)
  - **AND**
  - Polyneuropathy disability (PND) score IIIb or less or familial amyloid polyneuropathy (FAP) stage 2 or less
  - **AND**
  - Not used in combination with the following: TTR stabilizers (eg, tafamidis, diflunisal) and Onpattro™ (patisiran)
  - **AND**
  - Prescribed by or in consultation with a neurologist
  - **AND**
  - Dose prescribed is 284 mg injected subcutaneously once
**Drug** | **Medical Necessity**
---|---
| weekly

**Note: Clinical description of PND score**
- Score 0 = No symptoms
- Score I = Sensory disturbances but preserved walking capability
- Score II = Impaired walking capacity but ability to walk without a stick or crutches
- Score IIIA = Walking with the help of one stick or crutch
- Score IIIB = Walking with the help of two sticks or crutches
- Score IV = Confined to a wheelchair or bedridden

**Note: Clinical description of FAP stage**
- Stage 0 = No symptoms
- Stage 1 = Unimpaired ambulation
- Stage 2 = Assistance with ambulation required
- Stage 3 = Wheelchair-bound or bedridden

**Drug** | **Investigational**
---|---
Onpattro™ (patisiran) | All other uses of Onpattro™ and Tegsedi™ for conditions not outlined in this policy are considered investigational.
Tegsedi™ (inotersen)

**Approval** | **Criteria**
---|---
**Initial authorization** | Onpattro™ or Tegsedi™ may be approved up to 12 months.
**Re-authorization criteria** | • Continued therapy with Onpattro™ or Tegsedi™ will be approved for periods of one year if the above Onpattro™ or Tegsedi™ criteria are met and the patient has shown and continues to show efficacy documented in the medical record indicating positive clinical response (eg, improved or stable motor, neurologic, cardiac function, or serum TTR levels)
**AND**
• Improvement or stability in one of the following from baseline: PND score or FAP stage
**AND**
• Absence of treatment limiting toxicity

**Documentation Requirements**
The patient’s medical records submitted for review for all conditions should document that
**Documentation Requirements**

Medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the relevant history and physical evaluation information AND
- Documented TTR mutation verified by genetic testing AND
- Results of the PND score or FAP stage AND
- Dose and frequency of prescribed medication

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
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<tr>
<td>J3590</td>
<td>Unclassified biologics</td>
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</tbody>
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**Related Information**

**Consideration of Age**

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

**Benefit Application**

The drugs in this policy that are administered subcutaneously (Tegsedi™) are managed through the Pharmacy benefit. Drugs administered via IV infusion (Onpattro™) are managed through the Medical benefit.
Description

Hereditary transthyretin amyloidosis (hATTR), formerly known as familial amyloidotic polyneuropathy (FAP), is a rare, progressive disorder characterized by the extracellular deposition of TTR protein. hATTR can affect multiple organs and body systems, such as the heart, nervous system, gastrointestinal (GI) tract, and kidney. Symptoms may include autonomic dysfunction, GI dysfunction, ocular manifestation, cardiac manifestation, compromised renal function, or carpal tunnel syndrome. The most common mutation associated with hATTR is Val30Met. Although some mutations are associated mainly with polyneuropathy or cardiomyopathy, most patients have mixed clinical phenotypes. If untreated, death occurs about 10 years after onset of hATTR.

The disease course begins with unimpaired ambulation (FAP stage 1), then requiring ambulation (FAP stage 2), which proceeds to wheelchair confinement (FAP stage 3), where patients experience life-impacting symptoms including burning neuropathic pain, loss of sensation in hands and feet, diarrhea/constipation, sexual impotence, and dizziness/fainting. The median survival for patients with hATTR with polyneuropathy is reported as 5-15 years.

hATTR affects at least 10,000 people worldwide with about >120 TTR mutations being reported, with about 3,000-5,000 people in the U.S. However, symptoms of hATTR do not always start in one specific organ and the disease is often masked. As a result, these numbers may be underestimated due to under-diagnosis. Quantifying the disease burden in hATTR remains challenging since there is no single test that captures all the symptoms of the condition. Tests demonstrated that both mental and physical health in patients with hATTR were substantially lower than an age-match controlled group of patients not receiving treatment.

The protein TTR is synthesized and secreted by the liver, where it transports thyroxine and retinol. Mutations in TTR destabilize the protein, causing misfolding into a beta-pleated sheet configuration and forming insoluble amyloid fibrils. This mutation results in an autosomal dominant disorder primarily affecting the nerves and heart. With different mutations, symptomatic manifestations may vary even among family members.
Summary of Evidence

*Onpattro™ (patisiran)*

Fair quality evidence from the Phase 2 and APOLLO studies showed that patisiran 0.3 mg/kg intravenously (IV) every three weeks (Q3W) is effective in reducing transthyretin (TTR levels) and improving their modified neuropathy impairment scale+7 (mNIS+7) score, respectively, in adults diagnosed with hereditary transthyretin amyloidosis (hATTR) and neuropathy. The 0.3 mg/kg IV Q3W dosing regimen demonstrated the highest maximum TTR knockdown (KD) and TTR KD at nadir for both dose 1 (94.2% and 83.8%) and dose 2 (96.0% and 86.7%) compared to other dosing regimens (0.01, 0.05,0.15, and 0.3 mg/kg every four weeks [Q4W]). Patisiran showed significant improvement in patients’ change in mNIS+7 scores from baseline compared to placebo (-6.03 vs. 27.96), suggesting improvement in autonomic function. This is further proven in the Phase 2 open-label extension (OLE) trial, where patients were on patisiran for 24 months and had a change in mNIS+7 from baseline of -7.0. Secondary endpoints in the APOLLO trial saw improved scores as well, most notably in assessing quality of life using the Norfolk quality of life–diabetic neuropathy (QoL-DN) scale (-6.7 vs. 14.4).

Mild to moderate adverse events (AEs) were common in patisiran. Most AEs were infused-related reactions (IRRs), which occurred in 10.3% of patients in the Phase 2 trial and 18.9% of subjects in the patisiran group from the APOLLO trial. The Phase 2 OLE trial demonstrated similar results as well with 22.2% of subjects experiencing IRRs. Researchers attempted to prevent IRRs by pre-medicating patients with dexamethasone, acetaminophen, an H1 blocker, and an H2 blocker. As a result, pill burden may play a role in adherence and managing AEs. Another common AE was peripheral edema (29.7% in patisiran vs. 22.1% in placebo) which decreased over time with no patient needing to discontinue treatment. The Phase 2 trial reported one patient experiencing a urinary tract infection (UTI), sepsis, nausea, and vomiting. Another patient reported cellulitis, nausea, and vomiting. Because one patient experienced these symptoms, it is difficult to associate patisiran with these serious adverse events (SAEs). The APOLLO study had 36.5% of the patisiran group experience a SAE. The most common SAE found was diarrhea in 5.4% of patients. No increase in observed frequency of events for patisiran compared to placebo group by SOC.

*Tegsedi™ (inotersen)*

In the Phase III trial NEURO-TTR trial, inotersen treatment slowed the progression of polyneuropathy relative to placebo and stabilized neuropathy-related quality of life (QOL). The statistically significant treatment difference in mNIS+7 reflected progression in the placebo...
group and delayed progression in the inotersen group, though many inotersen patients reported improved neuropathy scores. Open-label extension (OLE) data suggest sustained delay of progression of polyneuropathy, though neuropathy-related QOL gain may not be durable. Cardiac endpoints did not differ statistically between the inotersen group and placebo group after 15 months of intervention; however, the trial was not powered to detect differences in cardiac outcomes. A small single-arm open label study shows minimal worsening of left ventricular mass.

Five deaths were reported during the study, all of which occurred in the inotersen group, through 15 months of treatment. Four deaths were considered related to disease progression and one death was considered possibly inotersen-related. Safety data show two key concerns with inotersen treatment: thrombocytopenia and glomerulonephritis. Frequent platelet and renal monitoring implemented during the Phase III NEURO-TTR trial suggests thrombocytopenia and decreased renal function may be manageable through enhanced monitoring. Adverse events considered related to treatment were more frequently reported by inotersen patients compared to placebo patients. Anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients. These antibodies typically develop after a median of 200 days of treatment and did not appear to affect drug efficacy, but patients with such antibodies reported more injection site reactions.

References

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>04/01/19</td>
<td>New policy, approved March 12, 2019. Add to Prescription Drug section. Onpattro (patisiran) and Tegsedi (inotersen) may be considered medically necessary when criteria are met. They are considered investigational for all other uses.</td>
</tr>
</tbody>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

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  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action before a deadline to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Deutsche (German):

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中文 (Chinese):
本通知有重要的讯息。本通知可能有关於您透過 Premera Blue Cross 提交的申請或保障的重要訊息。本通知内可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

037338 (07-2016)
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay nagalaman ng mahalagang impormasyon. Ang paunawa na ito ay mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring magaangalang ka na nagmagsagawa ng hakbang sa ilang mga itanakdang panahon unang mapananatili ang iyong pagsakop sa kalusugan o tulong na tumatagal o tumaluhan at iinaayon sa tulong na atiu i i'l lenaei fa'matala o le'ai ni fesoasoani e fa'amatala ona e malamalama i ai.

Thai (ไทย):
ประกาศนี้เป็นข้อความสำคัญที่เกี่ยวกับการดำเนินการของประกันสุขภาพของคุณ Premera Blue Cross และการใช้บริการในกรณีที่คุณต้องการ สำนักงานประกันสุขภาพที่เหมาะสมจะต้องจัดให้คุณทราบว่าการดำเนินการของประกันสุขภาพนี้ฉันให้คุณ คุณมีสิทธิ์ที่จะรับการช่วยเหลือและคำแนะนำที่สำคัญในการดำเนินการของประกันสุขภาพนี้ให้ได้.

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Це повідомлення містить важливу інформацію. Ця повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути важливі у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретній ситуації для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).