ONPATTRO® (patisiran) Lipid Complex Injection

ONPATTRO® (patisiran) lipid complex injection 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.

hATTR amyloidosis is a rare, underdiagnosed, inherited, rapidly progressive, debilitating and fatal disease.\(^1,3\)

The condition is caused by a variant in the transthyretin (TTR) gene that results in the accumulation of amyloid deposits at multiple sites in the body, including the nerves, heart, and gastrointestinal (GI) tract.\(^1,3\)

ONPATTRO is an RNAi (RNA interference) therapeutic designed to silence TTR messenger RNA, thereby reducing production of TTR protein. Reducing the serum TTR protein leads to a decrease in the amount of amyloid deposits that accumulate in tissues.\(^4\)

RNAi therapeutics are a new class of medicines designed to harness the natural biological process of RNAi.\(^5\)

ONPATTRO is the first FDA-approved RNAi therapeutic.

In APOLLO, the largest controlled study of hATTR amyloidosis completed to date, ONPATTRO was shown to improve polyneuropathy, as measured by the modified Neuropathy Impairment Score +7 (mNIS+7) — with reversal of neuropathy impairment in a majority of patients - and to improve quality of life, reduce autonomic symptoms, and improve ability to perform activities of daily living.\(^6\)

The most common side effects of ONPATTRO are respiratory infections, such as colds, sinus infections, and nasal congestion, and infusion-related reactions.\(^4,6\)

ONPATTRO is administered via intravenous (IV) infusion once every three weeks and the dose is based on actual body weight. Home administration may be an option for some patients after an evaluation and recommendation by the treating physician, and may not be covered by all insurance plans. Regardless of the setting, ONPATTRO infusions should be performed by a healthcare professional. For more information about ONPATTRO, please visit ONPATTRO.com.

ONPATTRO Clinical Profile at a Glance

- The FDA approval of ONPATTRO was based on positive results from the randomized, double-blind, placebo-controlled, global Phase 3 APOLLO study in hATTR amyloidosis patients with polyneuropathy.\(^6\)

- The primary endpoint of the APOLLO study was the change from baseline at 18 months in the modified Neuropathy Impairment Score +7 (mNIS+7), which assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure.\(^6\)
  - Patients treated with ONPATTRO had a mean 6.0-point decrease (improvement) in mNIS+7 from baseline compared to a 28.0-point mean increase (worsening) for patients in the placebo group, resulting in a 34.0-point mean difference relative to placebo, after 18 months of treatment.\(^4\)
  - Fifty-six percent of ONPATTRO-treated patients at 18 months of treatment experienced reversal of neuropathy impairment (a decrease from baseline in mNIS+7), compared to four percent of patients who received placebo.\(^4\)

- As measured by the Norfolk Quality of Life Diabetic Neuropathy (QOL-DN) Score, 51 percent of patients treated with ONPATTRO experienced improvement in quality of life at 18 months relative to their own baseline, compared to 10 percent of the placebo-treated patients.\(^6\)

- Over 18 months of treatment, patients treated with ONPATTRO experienced significant benefit vs. placebo for all other secondary efficacy endpoints including measures of activities of daily living, walking ability, nutritional status, and autonomic symptoms.\(^6\)

- The most common adverse events that occurred more frequently with ONPATTRO than with placebo were upper respiratory tract infections and infusion-related reactions. To reduce the risk of infusion-related reactions, patients received premedications prior to infusion.\(^4,6\)

Please see Important Safety Information on the next page.
About RNAi Therapeutics

- RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today. This discovery was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.

- By harnessing the natural biological process of RNAi occurring in our cells, a new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam’s RNAi therapeutic platform, function by silencing messenger RNA (mRNA) – the genetic precursors that encode for disease-causing proteins – thus reducing their production.

- The FDA approval of ONPATTRO® (patisiran) marked the arrival of RNAi therapeutics.

- ONPATTRO is the result of countless contributors who have overcome enormous scientific and business challenges to make RNAi therapeutics a reality.

Access to ONPATTRO: Alnylam Assist™

As part of Alnylam’s commitment to making therapies available, Alnylam Assist™ offers a range of personalized patient support services to patients prescribed ONPATTRO after a Start Form has been submitted, including helping patients understand their insurance coverage, financial assistance programs for eligible patients, educational materials to help facilitate conversations with doctors and family, and assistance with connecting to local resources. Patients will have access to Alnylam Case Managers and Alnylam Patient Education Liaisons throughout their treatment with ONPATTRO. Physicians and patients can learn more about Alnylam’s patient support program by visiting AlnylamAssist.com/ONPATTRO for more information.

IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory infections (29%) and infusion related reactions (19%).

For additional information about ONPATTRO, please see the full Prescribing Information.

References:

4. ONPATTRO Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.