ONPATTRO™ (patisiran)

Dosing and preparation guide

Indication

ONPATTRO™ (patisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Important Safety Information

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.

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

onpattro™ (patisiran) lipid complex injection

Hereditary ATTR amyloidosis is rapidly progressive and life-threatening[1-3]

Hereditary transthyretin-mediated (hATTR) amyloidosis is caused by a mutation in the transthyretin (TTR) gene that results in the accumulation of amyloid deposits in multiple organs of the body, including the nerves, heart, and GI tract.[1-3]

hATTR amyloidosis is a multisystem disease with heterogeneous symptom presentation[2]

Peripheral sensory-motor neuropathy
(e.g., neuropathic pain, paresthesia, weakness)

Autonomic dysfunction
(e.g., orthostatic hypotension, recurrent urinary tract infections)

GI manifestations
(e.g., diarrhea, nausea, vomiting)

Cardiovascular manifestations
(e.g., conduction abnormalities, arrhythmias, heart failure)

Symptoms of hATTR amyloidosis can progress quickly, leading to significant disability and dysfunction.[4,5]

GI=gastrointestinal.

Important Safety Information

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).

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

ONPATTRO™ (patisiran)–the first and only approved RNAi therapeutic[6]

ONPATTRO is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults[6]

- ONPATTRO is a double-stranded small interfering ribonucleic acid (siRNA) formulated as lipid nanoparticles for delivery to hepatocytes, the primary source of TTR protein in circulation[6,7]
- ONPATTRO is administered via intravenous (IV) infusion once every 3 weeks. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg[6]
- ONPATTRO is supplied as a 10 mg/5 mL solution in a single-dose glass vial[6]

ONPATTRO is a white to off-white, opalescent, homogeneous solution.[6] Note that there may be a white coating visible on the inner surface of the vial. This is normal and does not impact the product quality.

APOLLO study: Patients treated with ONPATTRO demonstrated a benefit versus placebo across all endpoints

- The mean serum TTR reduction after 18 months was 84%[6,7,a]
- Patients treated with ONPATTRO demonstrated significant improvement versus placebo in the modified Neuropathy Impairment Score +7 (mNIS+7), a composite measure of sensory, motor, and autonomic neuropathy[6]
- Patients treated with ONPATTRO also demonstrated significant improvement in quality of life, as measured by the Norfolk QoL-DN score versus placebo[6]

Norfolk QoL-DN=Norfolk Quality of Life-Diabetic Neuropathy.

[a]Evaluated in patients with hATTR amyloidosis treated with 0.3 mg/kg ONPATTRO via IV infusion once every 3 weeks.[6]

onpattro™ (patisiran) lipid complex injection

Preparation and dosing

To prepare ONPATTRO™ (patisiran), you will need:

- di(2-ethylhexyl)phthalate-free (DEHP-free) infusion bag containing 0.9% Sodium Chloride Injection, USP (normal saline solution). Total volume needed: 200 mL

  Important: If using a 250 mL infusion bag, it is necessary to remove the calculated volume of ONPATTRO plus 50 mL of normal saline to ensure that the total final volume is 200 mL

- 0.45 micron polyethersulfone (PES) syringe filter
- Empty sterile container (e.g., a glass vial or empty syringe)
- Syringes, needles, and standard IV preparation materials
- DEHP-free extension set with 1.2 micron PES in-line infusion filter (for administration of the infusion)

Dosing[6]

ONPATTRO is supplied as a 10 mg/5 mL solution in a single-dose glass vial.

ONPATTRO is administered via IV infusion once every 3 weeks.

Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg.

Use the dosing calculator on the back cover for quick, easy dosing calculations.

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

Premedication[6]

All patients should receive premedication prior to ONPATTRO™ administration to reduce the risk of IRRs.

Each of the following premedications should be given on the day of ONPATTRO infusion **at least 60 minutes prior to the start of infusion**:

- IV corticosteroid (e.g., dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- IV H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)
- IV H2 blocker (e.g., ranitidine 50 mg, or equivalent)

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions due to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (IV), or equivalent.

Some patients may require additional or higher doses of 1 or more of the premedications to reduce the risk of IRRs.

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.

Preparation and handling[6]

ONPATTRO™ (patisiran) must be filtered and diluted prior to IV infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

1. Remove ONPATTRO from the refrigerator and allow to warm to room temperature. Do not shake or vortex.

2. Inspect visually for particulate matter and discoloration. If the vials are discolored or foreign particles are present, do not use the vials and report the issue to Alnylam at 1-877-ALNYLAM.

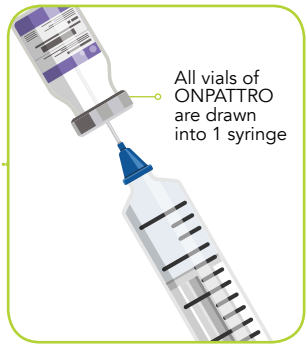
Note: ONPATTRO is a white to off-white, opalescent, homogeneous solution. A white coating may be observed on the inner surface of the vial, typically at the meniscus. This does not impact the quality of the drug. The coating may remain in the vial after withdrawing the solution. This also does not impact product quality.

3. Calculate the required dose of ONPATTRO based on the recommended weight-based dosage. **Please see the Dosing Calculator on the back cover**.

4. The final total volume of the ONPATTRO infusion is 200 mL. From the DEHP-free infusion bag containing 0.9% Sodium Chloride Injection, USP, remove the calculated volume of drug plus any extra saline.

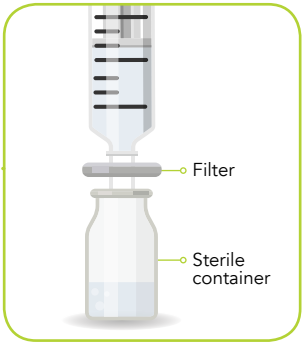
- If using a 250 mL infusion bag, it is necessary to remove the calculated volume of ONPATTRO plus 50 mL of normal saline

5. Withdraw the entire contents of all of the vials needed into a single sterile syringe.



Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

6. Filter ONPATTRO™ through a sterile 0.45 micron PES syringe filter into a sterile container. **Do not filter the drug out of the vial directly into an IV bag.**

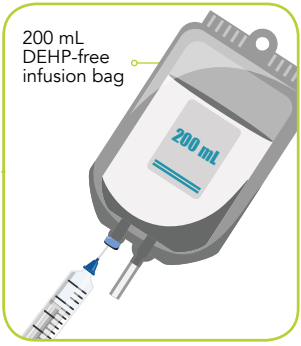


7. Withdraw the calculated dose (see step 3) of filtered ONPATTRO from the sterile container using a new sterile syringe.

8. Dilute the required volume of filtered ONPATTRO into the DEHP-free infusion bag containing 0.9% Sodium Chloride Injection, USP.

9. Gently invert the infusion bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.

10. Discard any unused portion of ONPATTRO.



Important Safety Information

Adverse Reactions

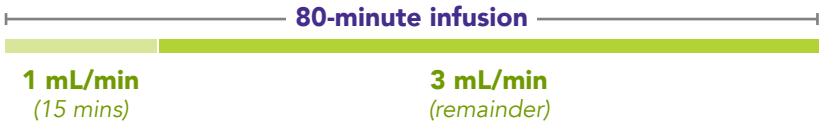
The most common adverse reactions that occurred in patients treated with ONPATTRO were upper respiratory tract infections (29%) and infusion-related reactions (19%).

Administration[6]

The steps below provide the instruction you'll need to administer ONPATTRO™ (patisiran):

1. Use a dedicated line with an infusion set containing a 1.2 micron PES in-line infusion filter. Use infusion sets and lines that are DEHP-free.

2. Infuse the diluted solution of ONPATTRO intravenously, via an ambulatory infusion pump, over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then increase to approximately 3 mL/min for the remainder of the infusion.



The duration of infusion may be extended in the event of an IRR. **See page 10 for details about what to do in the case of IRRs**.

3. Administer only through a free-flowing venous access line. Monitor the infusion site for possible infiltration during drug administration. Suspected extravasation should be managed according to local standard practice for nonvesicants.

4. After completion of the infusion, flush the IV administration set with 0.9% Sodium Chloride Injection, USP, to ensure that all ONPATTRO has been administered.

Observe the patient during the infusion and, if clinically indicated, following the infusion.

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

Considerations when preparing the dose

Proper preparation of ONPATTRO™ requires filtration to remove particulates. An additional vial of ONPATTRO may be required depending on the type of filter used and the amount of product that remains in the filter (hold-up volume).[6] The dosing calculator found on the back cover assumes that 1 mL of drug product remains in the filter when determining the number of vials needed, based on the manufacturer's information for the Pall PharmAssure® 0.45 micron 32 mm syringe filter with low protein binding Supor® membrane (HP4644).[9]

The diluted solution should be administered immediately after preparation.

- If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time)
- Do not freeze

Missed dose[6]

If a dose is missed, administer ONPATTRO as soon as possible.

- If ONPATTRO is administered within 3 days of the missed dose, continue dosing according to the patient's original schedule
- If ONPATTRO is administered more than 3 days after the missed dose, continue dosing every 3 weeks thereafter

Important Safety Information

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).

Infusion-related reactions[6]

IRRs have been observed in patients treated with ONPATTRO™ (patisiran).

In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a double-blind, placebo-controlled study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients.

- Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time
- Across clinical studies, the most common symptoms (reported in ≥2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache
- One patient in the ONPATTRO Expanded Access Program had a severe adverse reaction of hypotension and syncope during an ONPATTRO infusion
- IRRs resulted in permanent discontinuation of ONPATTRO in <1% of patients in clinical studies
- If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment) as clinically indicated

If a patient has a mild to moderate IRR that requires interruption of the infusion, consider resuming the infusion at a slower rate only if symptoms have resolved.

- In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of 1 or more of the premedications with subsequent infusions to reduce the risk of IRRs.

To report suspected adverse reactions, contact Alnylam Pharmaceuticals at 1-877-ALNYLAM (1-877-256-9526), or the FDA at 1-800-FDA-1088, or go to www.fda.gov/medwatch.

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

Storage and handling[6]

- Store ONPATTRO™ vials at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen
- If refrigeration is not available, ONPATTRO vials can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days

After preparation:

ONPATTRO does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to 16 hours (including infusion time). Do not freeze.

Consider home infusion

Home infusion may be an option for some patients. The decision for a patient to receive home infusions should be made after an evaluation and recommendation by the treating physician, and may not be covered by all insurance plans. Some physicians may choose to have patients receive their first few infusions in the clinic prior to transitioning to home infusion. Regardless of the setting, ONPATTRO infusions should be performed by a healthcare professional.

Your patient's Alnylam Assist Case Manager can help answer questions about home infusion.

Ongoing support from Alnylam Assist™

Alnylam Assist offers a wide range of services to guide your patients through treatment with ONPATTRO, including:

- Disease education and support for your patients that is customized to their communication preferences
- Comprehensive, patient-specific benefit verification and reimbursement education
- Ordering assistance and facilitation of delivery via specialty distributor or specialty pharmacy

Alnylam ASSIST™

8AM–7PM ET, Monday–Friday
: 1-833-256-2748 | : 1-833-256-2747

To learn more visit www.AlnylamAssist.com.

onpattro™ (patisiran) lipid complex injection

Dosing and preparation FAQs

1. Are substitutions permitted for the IV premedications? Can they be given orally?
IV equivalents of dexamethasone, diphenhydramine, and ranitidine may be used per the judgment of the prescribing physician. For premedications not available or not tolerated intravenously, equivalents may be administered orally.[6]

2. What is the white coating in the ONPATTRO™ (patisiran) vial?
ONPATTRO is a white to off-white, opalescent, homogeneous solution. Some of the product residue may be observed on the inner surface of the vial, typically at the meniscus. This coating may remain in the vial after withdrawing the solution and does not impact the quality of the drug.[6]

3. How many vials of ONPATTRO are needed to prepare my patient's dose?
ONPATTRO is administered via IV infusion once every 3 weeks. Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg. ONPATTRO is supplied as a 10 mg/5 mL (2 mg/mL) solution in a single-dose vial and proper preparation requires filtration to remove particulates. An additional vial of ONPATTRO may be required to prepare the full recommended dose, depending on the type of filter used and the amount of product that remains in the filter (hold-up volume). Consult the filter manufacturer to determine the expected hold-up volume for the filter used at your pharmacy to prepare the ONPATTRO dose. The Dosing Calculator on the back cover of this guide assumes that 1 mL of drug product remains in the filter when determining the number of vials needed.[6,9]

4. What size IV bag is needed to prepare ONPATTRO?
The final total volume of the prepared ONPATTRO dose is 200 mL. If using a 250 mL infusion bag, it is necessary to remove the calculated dose of ONPATTRO plus 50 mL of normal saline to ensure that the total final volume is 200 mL.

5. Can I filter ONPATTRO directly out of the vial and into the infusion bag?
ONPATTRO must be withdrawn into a sterile syringe from the vial and then filtered through a 0.45 micron PES syringe filter into a sterile container. Filtering ONPATTRO directly out of the vial would cause shearing of the lipid nanoparticles due to increased pressure and therefore is not recommended.[6]

6. What should I use for a sterile container during step 6, on page 7?
Options for sterile containers include glass containers or vials, and sterile syringes.[6]

Please see Important Safety Information on the following pages and accompanying Full Prescribing Information.

7. Can a different size PES filter be used during step 6, on page 7?
In the APOLLO study, a 0.2 micron PES filter was used to prepare ONPATTRO™. If 0.45 micron PES filters are unavailable, a 0.2 micron PES filter can be used; however, each vial of ONPATTRO will require filtration through a separate 0.2 micron filter due to the smaller pore size.

8. Why does ONPATTRO preparation require 2 filtration steps?
The protocol for preparation of ONPATTRO includes filtering the drug through a PES filter prior to diluting in an infusion bag of normal saline. The prepared drug is then infused from the bag through a second in-line PES filter of 1.2 micron pore size. These 2 filtration steps assure delivery of ONPATTRO without residual particles that could cause filter-clogging events during the infusion.

9. What should be done if my patient experiences an infusion-related reaction during the ONPATTRO infusion?
If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management if clinically indicated. If the infusion is interrupted, consider resuming at a slower rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.[6]

For additional questions regarding ONPATTRO, please contact Alnylam Medical Information at 1-877-ALNYLAM (1-877-256-9526) or medinfo@alnylam.com. An electronic version of the Dosing & Preparation Guide, plus additional resources for patients and healthcare professionals can be found at www.ONPATTRO.com.

Indication

ONPATTRO™ (patisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Important Safety Information

Infusion-Related Reactions

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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 tract infections (29%) and infusion-related reactions (19%).

Please see the accompanying Full Prescribing Information for additional information.

References: 1. Adams D, Coelho T, Obici L, et al. *Neurology*. 2015;85(8):675-682. **2.** Conceição I, González-Duarte A, Obici L, et al. *J Peripher Nerv Syst*. 2016;21(1):5-9. **3.** Shin SC, Robinson-Papp J. *Mt Sinai J Med*. 2012;79(6):733-748. **4.** Ando Y, Coelho T, Berk JL, et al. *Orphanet J Rare Dis*. 2013;8:31. **5.** Dharmarajan K, Maurer MS. *J Am Geriatr Soc*. 2012;60(4):765-774. **6.** ONPATTRO [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; 2018. **7.** Gertz MA. *Am J Manag Care*. 2017;23(7 suppl):S107-S112. **8.** Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. *N Engl J Med*. 2018;379(1):11-21. **9.** PharmAssure 32 mm syringe filters [manufacturing leaflet]. Port Washington, NY: Pall Corporation; 2010.

Dosing Calculator

ONPATTRO™ is supplied as a 10 mg/5 mL solution in a single-dose vial.

ONPATTRO is administered via IV infusion once every 3 weeks.

Dosing is based on actual body weight. For patients weighing <100 kg, the recommended dose is 0.3 mg/kg. For patients weighing ≥100 kg, the recommended dose is 30 mg.

Proper preparation of ONPATTRO requires filtration to remove particulates. An additional vial of ONPATTRO may be required depending on the type of filter used and the amount of product that remains in the filter (hold-up volume). **The dosing calculator below assumes that 1 mL of drug product remains in the filter when determining the number of vials needed**, based on the available manufacturer's information for the Pall PharmAssure® 0.45 micron 32 mm syringe filter with low protein binding Supor® membrane (HP4644).[9]

Dosing Calculator

Note: The bolded numbers signify weights that may require an additional vial of ONPATTRO™ (patisiran) due to drug product remaining in the filter.

25–49 kg

Body Weight (kg)	mL	Vials
25	3.75	1
26	3.9	1
27	4.05	**2**
28	4.2	**2**
29	4.35	**2**
30	4.5	**2**
31	4.65	**2**
32	4.8	**2**
33	4.95	**2**
34	5.1	2
35	5.25	2
36	5.4	2
37	5.55	2
38	5.7	2
39	5.85	2
40	6	2
41	6.15	2
42	6.3	2
43	6.45	2
44	6.6	2
45	6.75	2
46	6.9	2
47	7.05	2
48	7.2	2
49	7.35	2

50–74 kg

Body Weight (kg)	mL	Vials
50	7.5	2
51	7.65	2
52	7.8	2
53	7.95	2
54	8.1	2
55	8.25	2
56	8.4	2
57	8.55	2
58	8.7	2
59	8.85	2
60	9	2
61	9.15	**3**
62	9.3	**3**
63	9.45	**3**
64	9.6	**3**
65	9.75	**3**
66	9.9	**3**
67	10.05	3
68	10.2	3
69	10.35	3
70	10.5	3
71	10.65	3
72	10.8	3
73	10.95	3
74	11.1	3

75–99 kg

Body Weight (kg)	mL	Vials
75	11.25	3
76	11.4	3
77	11.55	3
78	11.7	3
79	11.85	3
80	12	3
81	12.15	3
82	12.3	3
83	12.45	3
84	12.6	3
85	12.75	3
86	12.9	3
87	13.05	3
88	13.2	3
89	13.35	3
90	13.5	3
91	13.65	3
92	13.8	3
93	13.95	3
94	14.1	**4**
95	14.25	**4**
96	14.4	**4**
97	14.55	**4**
98	14.7	**4**
99	14.85	**4**

onpattro™ (patisiran) lipid complex injection