PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**ONPATTRO™**

Patisiran Lipid Complex for Injection

Lipid complex solution; 2 mg/mL Patisiran (as patisiran sodium); intravenous

ATC Code N07XX12
Other nervous system drugs

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ONPATTRO (patisiran) is indicated for the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ONPATTRO have not been studied in pediatric patients < 18 years of age. Therefore, Health Canada has not authorized an indication for pediatric use.

2 CONTRAINDICATIONS

ONPATTRO (patisiran) is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylaxis or anaphylactoid reactions) to patisiran or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- ONPATTRO (patisiran) should be administered by a healthcare professional.
- **Premedications should be administered (see Required Premedication).**
- **Administer only as an intravenous infusion after dilution (see Administration).**

3.2 Recommended Dose and Dosage Adjustment

The recommended dose of ONPATTRO is 0.3 mg/kg administered via intravenous (iv) infusion once every 3 weeks.

Dosing is based on body weight, to a maximum dose of 30 mg. For patients weighing ≥ 100 kg, the recommended dose of ONPATTRO should not exceed 30 mg.

Pediatric patients: Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age): No dose adjustment is required in patients ≥ 65 years old (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic impairment: No dose adjustment is necessary in patients with mild hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

Liver transplant: ONPATTRO has not been studied in patients with prior liver transplant.

Renal impairment: No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73m^2) (see

ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

Required Premedication
All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs) (see WARNINGS AND PRECAUTIONS, Infusion-Related Reactions). Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- Intravenous corticosteroid (dexamethasone 10 mg, or equivalent)
- Oral acetaminophen (500 mg)
- Intravenous H1 blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous H2 blocker (ranitidine 50 mg, or equivalent)

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

If clinically indicated, the corticosteroid may be tapered to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent, for patients who are tolerating their infusions well.

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed (see WARNINGS AND PRECAUTIONS, Infusion-Related Reactions).

3.3 Administration

- Dilute ONPATTRO prior to intravenous infusion (see DOSAGE AND ADMINISTRATION, Preparation of Intravenous Infusion).
- Use a dedicated line with an infusion set containing a 1.2 micron polyethersulfone (PES) in-line infusion filter. Use infusion sets and lines that are di(2-ethylhexyl)phthalate-free (DEHP-free).
- Infuse the diluted solution of ONPATTRO intravenously over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, then, if well tolerated, 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 WARNINGS AND PRECAUTIONS, Infusion-Related Reactions).
- 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 non-vesicants.
- Observe the patient during the infusion and, if clinically indicated, following the infusion (see WARNINGS AND PRECAUTIONS, Infusion-Related Reactions).
- After completion of the infusion, flush the intravenous administration set with 0.9% sodium chloride solution to ensure that all ONPATTRO has been administered.

3.4 Preparation of Intravenous Infusion

ONPATTRO must be diluted prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

- Remove ONPATTRO from the refrigerator. Do not shake or vortex.
- Inspect visually for particulate matter and discoloration. Do not use if discoloration or foreign particles are present. ONPATTRO is a white to off-white, opalescent, homogeneous

solution. A white to off-white coating may be observed on the inner surface of the vial, typically at the liquid-headspace interface. Product quality is not impacted by presence of the white to off-white coating.

- Calculate the required volume of ONPATTRO based on the recommended weight-based dosage, to a maximum of 15mL (30mg) (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).
- Withdraw the entire contents of one or more vials into a single sterile syringe.
- Filter ONPATTRO through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.
- Withdraw the required volume of filtered ONPATTRO from the sterile container using a sterile syringe.
- Dilute the required volume of filtered ONPATTRO into an infusion bag containing 0.9% sodium chloride solution for a total volume of 200 mL. Use infusion bags that are DEHP-free.
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.
- Discard unused portion of ONPATTRO.
- Inspect the infusion bag visually for particulate matter and discoloration prior to administration. DO NOT use if solution contains particles.
- Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired.
- 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 (15°C to 30°C) for up to 16 hours (including infusion time). Do not freeze.

3.5 Missed Dose

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.

4 OVERDOSAGE

Reported experience with overdose is limited. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	2 mg of patisiran per 1 mL	• Cholesterol • DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate) • DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine) • PEG_{2000}-C-DMG (α-(3'-{[1,2-di(myristyloxy) propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene) • Potassium phosphate, monobasic, anhydrous • Sodium chloride • Sodium phosphate, dibasic, heptahydrate • Water for injection

ONPATTRO contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA), formulated as lipid nanoparticles for delivery to hepatocytes.

ONPATTRO contains 10.5 mg patisiran sodium equivalent to 10 mg patisiran free acid in 5 mL per vial. ONPATTRO is a sterile, preservative-free, white to off-white, opalescent, homogeneous solution for intravenous infusion. ONPATTRO is supplied in a single-use, 10 mL Type I glass vial with a Flurotec®-coated chlorobutyl stopper and an aluminum flip-off cap containing 5 mL of solution at a concentration of 2 mg of patisiran per 1 mL. The Flurotec®-coated stopper is not made with natural rubber latex.

ONPATTRO is available in cartons containing one single-use vial each.

6 WARNINGS AND PRECAUTIONS

General

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO (patisiran). In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and H1 and H2 blockers to reduce the risk of IRRs. In a double-blind placebo-controlled study, called APOLLO, 18.9% of ONPATTRO-treated patients experienced IRRs, compared to 9.1% of placebo-treated patients. In ONPATTRO-treated patients, all IRRs were either mild (95.2%) or moderate (4.8%) in severity. Among ONPATTRO-treated patients who experienced an IRR, 78.6% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. Few IRRs led to infusion interruption. IRRs resulted in permanent discontinuation of ONPATTRO in < 1% of patients in clinical studies. 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 (see ADVERSE REACTIONS).

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion (see DOSAGE AND ADMINISTRATION, Required Premedication). If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management (e.g. corticosteroids or other symptomatic treatment) as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate after symptoms have resolved. Discontinue the ONPATTRO infusion in the case of a serious or life-threatening IRR.

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

Reduced Serum Vitamin A Levels and Recommended Supplementation
By reducing serum TTR protein, ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily amount of vitamin A is advised for patients taking ONPATTRO. Serum vitamin A levels should not be used to guide vitamin A supplementation during treatment with ONPATTRO (see DRUG INTERACTIONS, Drug-Laboratory Test Interactions, and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Particular care should be taken by women of child-bearing potential and during early stages of pregnancy as levels of serum vitamin A too low or too high may increase the risk of fetal malformations.

Ocular changes may occur in patients with hATTR amyloidosis due to amyloid deposition in the eye. If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended.

Driving and Operating Machinery
No studies of the effects on the ability to drive or operate machinery during treatment with ONPATTRO have been performed.

Sexual Health
Reproduction
Due to the potential teratogenic risk arising from unbalanced vitamin A levels, it is recommended that women of child-bearing potential use effective contraception during treatment with ONPATTRO and for 12 weeks after stopping treatment.

Fertility
There are no data on the effects of ONPATTRO on human fertility. No impact on male or female fertility was detected in animal studies (see NON-CLINICAL TOXICOLOGY).

6.1 Special Populations

6.1.1 Pregnant Women

There are no data on the use of ONPATTRO in pregnant women. The effects of a reduction in maternal serum TTR or serum vitamin A levels on the fetus are unknown (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). ONPATTRO is not recommended for use during pregnancy (see above, Reduced Serum Vitamin A Levels and Recommended Supplementation).

During the first 60 days of pregnancy, too high or too low vitamin A levels may both be associated with an increased risk of fetal malformation. Therefore, pregnancy should be ruled out before initiating ONPATTRO. Women of childbearing potential should practice effective contraception while receiving ONPATTRO. If a woman intends to become pregnant, ONPATTRO and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and seen to have returned to normal before conception is attempted.

In the event of an unplanned pregnancy, ONPATTRO should be discontinued.

No adverse effects on pregnancy or embryo-fetal development were observed with weekly administration of ONPATTRO, at 0.8 and 0.6 times the recommended human dose [RHD] unadjusted for dosing schedule to rats and rabbits, respectively. However, spontaneous abortions, reduced embryo-fetal survival, and reduced fetal body weights were observed in rabbits at HED 1.1 times the RHD, unadjusted for dosing schedule. No significant placental transfer was detected in rats or rabbits (see NON-CLINICAL TOXICOLOGY, Teratogenicity).

6.1.2 Breast-feeding

There is no information regarding the presence of ONPATTRO in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not present in milk, although small amounts of the lipid components DLin-MC3-DMA and PEG_{2000}-C-DMG were present in milk (see NON-CLINICAL TOXICOLOGY, Teratogenicity).

6.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ONPATTRO have not been studied in children or adolescents < 18 years of age. Therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

No dose adjustment is required in patients ≥ 65 years old (see ACTION AND CLINICAL PHARMACOLOGY, Geriatrics). No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

In placebo-controlled and open-label clinical studies, a total of 224 patients with hATTR amyloidosis received ONPATTRO (patisiran) for a median of 2.2 years, with some individuals receiving exposure to ONPATTRO for up to 4.1 years. Of these 224 patients, 186 patients received ≥ 1 year of treatment, 137 patients received ≥ 2 years of treatment, and 52 patients received ≥ 3 years of treatment.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Placebo-controlled study
In the pivotal, placebo-controlled study, called APOLLO, 148 patients received 0.3 mg/kg ONPATTRO and 77 patients received placebo administered once every 3 weeks via intravenous infusion for up to 18 months, with a mean ONPATTRO exposure of 17.7 months. All patients received premedication with a corticosteroid, acetaminophen, and H1 and H2 blockers (see DOSAGE AND ADMINISTRATION, Required Premedication).

The most frequently occurring adverse reactions reported in ONPATTRO-treated patients (≥ 10% of patients and occurring ≥ 3 percentage points more frequently than in placebo-treated patients) were peripheral edema and infusion-related reactions. The only adverse reaction resulting in the discontinuation of ONPATTRO was an infusion-related reaction (1 patient, 0.7%).

The safety profile of ONPATTRO was generally consistent across all subgroups including age, sex, race, weight, geographic region, V30M mutation status, disease stage, and patients that met pre-defined criteria for cardiac involvement, i.e., having baseline left ventricular (LV) wall thickness ≥ 13 mm, with no history of hypertension or aortic valve disease.

Adverse reactions for ONPATTRO are defined as those adverse events occurring at a ≥ 3 percentage point higher frequency in patients treated with ONPATTRO, compared with placebo, and other potentially relevant adverse events based on other studies with ONPATTRO. The adverse reactions are presented as MedDRA preferred terms (MedDRA version 18.0), sorted under the respective System Organ Class (SOCs) (Table 2).

Table 2: Adverse Reactions that Occurred at a ≥ 3 Percentage Point Higher Frequency with ONPATTRO Compared to Placebo in the APOLLO Trial

System Organ Class	Preferred term	ONPATTRO N=148 %	Placebo N=77 %
General disorders and administration site conditions	Peripheral edema	30	22
Immune System disorders	Infusion-related reaction [a]	19	9
Gastrointestinal disorders	Dyspepsia	8	4
Musculoskeletal and connective tissue disorders	Muscle spasms	8	1
	Arthralgia	7	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	7	0
Skin and subcutaneous tissue disorders	Erythema	7	3

System Organ Class	Preferred term	ONPATTRO N=148 %	Placebo N=77 %
Infections and infestations	Bronchitis	6	3
	Rhinitis	4	0
	Sinusitis	4	0
Ear and labyrinth disorders	Vertigo	5	1

[a] Infusion-related reaction symptoms include but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.

7.3 Less Common Clinical Trial Adverse Reactions

Extravasation
Extravasation was observed in < 0.5% of infusions in clinical studies. Signs and symptoms included phlebitis or thrombophlebitis, infusion or injection site swelling, dermatitis (subcutaneous inflammation), cellulitis, erythema or injection site redness, burning sensation, or injection site pain.

Immunogenicity
Anti-drug antibodies to ONPATTRO were evaluated by measuring antibodies specific to PEG_{2000}-C-DMG, a lipid component exposed on the surface of ONPATTRO. In the placebo-controlled and open-label clinical studies, 7 of 194 (3.6%) patients with hATTR amyloidosis developed anti-drug antibodies, as measured during treatment with ONPATTRO. One additional patient had pre-existing anti-drug antibodies. Anti-drug antibody titers were low and transient with no evidence of an effect on clinical efficacy, the safety profile, or the pharmacokinetic or pharmacodynamic profiles of ONPATTRO.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ONPATTRO with the incidence of antibodies to other products may be misleading.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

No formal clinical drug interaction studies have been performed. ONPATTRO (patisiran) is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes. The components of ONPATTRO are not inhibitors or inducers of cytochrome P450 enzymes or transporters, except for time-dependent inhibition and weak induction of CYP2B6 in vitro. The net effect on CYP2B6 substrates (e.g., bupropion and efavirenz) in vivo is unknown. Patisiran is not a substrate of cytochrome P450 enzymes. In a population pharmacokinetic analysis, concomitant use of strong or moderate CYP3A inducers and inhibitors did not impact the pharmacokinetic parameters of patisiran.

8.2 Drug-Food Interactions

Interactions with food have not been established.

8.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.4 Drug-Laboratory Test Interactions

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with ONPATTRO reduces serum TTR levels, which results in reduced levels of retinol binding protein and vitamin A in the serum. However, transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. As a result, laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation during treatment with ONPATTRO (See WARNINGS AND PRECAUTIONS, Reduced Serum Vitamin A Levels and Recommended Supplementation and ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

In patients with hATTR amyloidosis, (See USAGE OF hATTR AMYLOIDOSIS IN INDICATIONS) serum mutant and wild-type TTR proteins form amyloid deposits in tissues leading to progressive polyneuropathy and cardiomyopathy. ONPATTRO contains patisiran, a double-stranded siRNA that specifically targets a genetically conserved sequence in the 3' untranslated region of all mutant and wild-type TTR mRNA. Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through a natural process called RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA, resulting in reduced serum TTR protein. In animal studies, patisiran-mediated reductions in TTR mRNA resulted in reduced serum TTR protein.

9.2 Pharmacodynamics

The pharmacodynamic effects of ONPATTRO were evaluated in hATTR amyloidosis patients treated with 0.3 mg/kg ONPATTRO via intravenous infusion once every 3 weeks.

Mean serum TTR was reduced by approximately 80% within 10 to 14 days after a single dose. With repeat dosing every 3 weeks, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 84%, respectively. The mean maximum reduction of serum TTR over 18 months was 88%. Similar TTR reductions were observed regardless of TTR mutation, sex, age, or race. In an ongoing open-label extension study, serum TTR reduction was maintained up to 3 years with continued dosing. In a dose-ranging study, greater TTR reduction was maintained over the dosing interval with the recommended dosing regimen of 0.3 mg/kg every 3 weeks compared to 0.3 mg/kg every 4 weeks.

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Mean reductions in serum retinol binding protein of 45% and serum vitamin A of 62% were observed over 18 months (see WARNINGS AND PRECAUTIONS, Reduced Serum

Vitamin A Levels and Recommended Supplementation and DRUG INTERACTIONS, Drug-Laboratory Test Interactions).

Cardiac electrophysiology
Formal QTc studies have not been conducted with ONPATTRO. Based on its physicochemical properties, ONPATTRO has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical studies to suggest that ONPATTRO delays ventricular repolarization.

9.3 Pharmacokinetics

The pharmacokinetic properties of ONPATTRO were characterised by measuring the plasma concentrations of patisiran and the lipid components DLin-MC3-DMA and PEG_{2000}-C-DMG.

Table 3 - Summary of ONPATTRO Pharmacokinetic Parameters in Patients with hATTR Amyloidosis Following 0.3mg/kg Intravenous Administration Every 3 Weeks

Analytes	C_{max}[a]	C_{trough}[a]	AUC_{τ}[a]
Patisiran	7.15 ± 2.14 µg/mL	0.021 ± 0.044 µg/mL	184 ± 159 µg·h/mL
DLin-MC3-DMA	40.2 ± 11.5 µg/mL	1.75 ± 0.698 µg/mL	1403 ± 514 µg·h/mL
PEG_{2000}-C-DMG	4.22 ± 1.22 µg/mL	0.0236 ± 0.0093 µg/mL	145 ± 64.7 µg·h/mL

[a]Steady state with every 3 weeks dosing, mean ± SD

Absorption: Greater than 95% of patisiran in the circulation is associated with lipid nanoparticles. At the recommended dose regimen of 0.3 mg/kg every 3 weeks, steady state was reached by 24 weeks of treatment. The estimated mean ± SD steady state peak concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_{τ}) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_{τ} was 3.2-fold at steady state compared to the first dose.

Patisiran exposure increased proportionally with increase in dose over the range evaluated in clinical studies (0.01 to 0.5 mg/kg). Patisiran exhibits linear and time-independent pharmacokinetics with chronic dosing at the recommended dose regimen of 0.3 mg/kg every 3 weeks.

Distribution: Plasma protein binding of ONPATTRO is low, with ≤ 2.1% binding observed *in vitro* with human serum albumin and human α1-acid glycoprotein. ONPATTRO distributes primarily to the liver. Minimal distribution was detected in the central nervous system and heart. At the recommended dose regimen of 0.3 mg/kg every 3 weeks, the mean ± SD steady-state volume of distribution of patisiran (V_{ss}) was 0.26 ± 0.20 L/kg. The mean ± SD volume of distribution of DLin-MC3-DMA and of PEG_{2000}-C-DMG was 0.47 ± 0.24 L/kg and 0.13 ± 0.05 L/kg, respectively.

Metabolism: The siRNA component of patisiran is metabolized by nucleases to nucleotides of various lengths. DLin-MC3-DMA is primarily metabolized to 4-dimethylaminobutyric acid (DMBA) by hydrolysis. There is little to no metabolism of PEG_{2000}-C-DMG.

Elimination: At the recommended dose regimen of 0.3 mg/kg every 3 weeks, mean ± SD

steady state plasma clearance (CL_{ss}) of patisiran was 3.0 ± 2.5 mL/h/kg. The mean ± SD terminal elimination half-life ($t_{1/2\beta}$) was 3.2 ± 1.8 days. Less than 1% of patisiran in the administered dose was recovered intact in urine.

The estimated DLin-MC3-DMA mean ± SD steady-state CL_{ss} was 2.1 ± 0.8 mL/h/kg. Approximately 5.5% of DLin-MC3-DMA was recovered after 96 hours as its metabolite (DMBA) in urine.

The estimated PEG_{2000}-C-DMG mean ± SD steady-state CL_{ss} was 2.1 ± 0.6 mL/h/kg. In rats and monkeys, PEG_{2000}-C-DMG is eliminated unchanged in the bile. PEG_{2000}-C-DMG excretion in humans was not measured.

Special Populations and Conditions

Pediatrics: The safety and efficacy of ONPATTRO have not been studied in children or adolescents <18 years old. Therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics: In the placebo-controlled study, 62 (41.9%) patients treated with ONPATTRO were ≥ 65 years old and 9 (6.1%) patients were ≥ 75 years old. There were no significant differences in steady state pharmacokinetic parameters or TTR reduction between patients < 65 years old and ≥ 65 years old.

Sex and race: Clinical studies did not identify significant differences in steady state pharmacokinetic parameters or TTR reduction based on sex or race (non-Caucasian vs. Caucasian).

Hepatic Impairment: Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild hepatic impairment (bilirubin ≤ 1 x ULN and AST > 1 x ULN, or bilirubin > 1.0 to 1.5 x ULN and any AST) on patisiran exposure or TTR reduction compared to patients with normal hepatic function. ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

Renal Impairment: Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73m^2) on patisiran exposure or TTR reduction compared to subjects with normal renal function. ONPATTRO has not been studied in patients with severe renal impairment or end-stage renal disease.

10 STORAGE, STABILITY AND DISPOSAL

Temperature
Store under refrigeration (2 to 8 ºC).
Do not freeze. Discard vial if it has been frozen.

If refrigeration is not available, ONPATTRO can be stored at room temperature up to 25°C for up to 14 days.

Other
For storage conditions of ONPATTRO after dilution in the infusion bag, see DOSAGE AND ADMINISTRATION, Preparation of Intravenous Infusion).

11 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

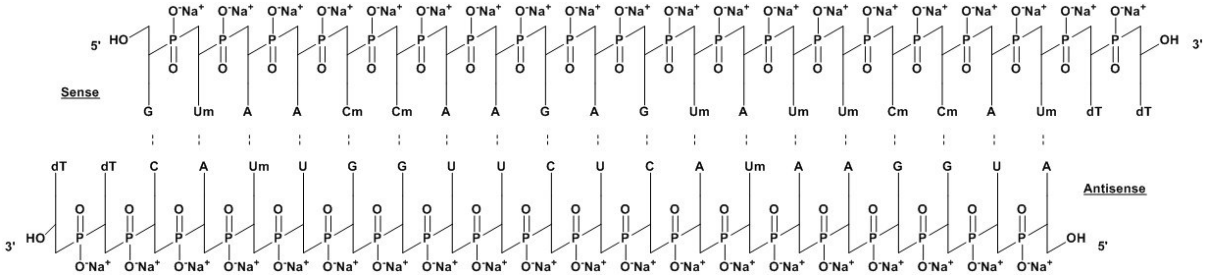
12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name/USAN/Common name: patisiran

Molecular formula and molecular mass: The molecular formula of patisiran is C_{412} H_{520} N_{148} O_{290} P_{40} and the molecular weight is 13424 Da.

Structural formula:



A, adenosine; C, cytidine; G, guanosine; U, uridine; Cm, 2'-*O*-methylcytidine; Um, 2'-*O*-methyluridine; dT, thymidine

Physicochemical properties:

- The solubility of patisiran drug substance in water and phosphate buffered saline has been determined to be at least 220 mg/mL
- pH of a 1% solution in KCl: 5.0 – 7.5
- pKa of ~6.5

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 4 –Summary of Patient Demographics in the APOLLO Trial

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age Years (Range)	Sex
Global, randomized (2:1), double-blind, placebo-controlled	0.3 mg/kg, via intravenous infusion once every 3 weeks, for 18 months	patisiran: 148 placebo: 77	62 (24, 83)	Male (74%) Female (26%)

The efficacy of ONPATTRO (patisiran) was demonstrated in a global, randomized, double-blind, placebo-controlled study in 225 patients with hATTR amyloidosis having a TTR mutation and symptomatic polyneuropathy. Patients were randomized 2:1 to receive 0.3 mg/kg ONPATTRO or placebo via intravenous infusion once every 3 weeks for 18 months. All patients received premedication with a corticosteroid, acetaminophen, and H1 and H2 blockers.

In the study, 148 patients received patisiran and 77 patients received placebo. The median patient age at baseline was 62 (range: 24 to 83) years. 74% of patients were male, 26% were

female. The majority of patients were Caucasian (72%), followed by Asian (23%), Black (2%), and Other (2%). Patients were from Western Europe (44%), North America (21%), Asia (20%), Central and South America (8%), or Eastern Europe (8%). Thirty-nine (39) different TTR mutations were represented; the most common (≥ 5%) were V30M (43%), A97S (9%), T60A (7%), E89Q (6%), and S50R (5%). Approximately 10% of patients had the V30M mutation and early onset of symptoms (< 50 years old). At baseline, 46% of patients had Stage 1 disease (unimpaired ambulation; mostly mild sensory, motor and autonomic neuropathy in the lower limbs), and 53% had Stage 2 disease (assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk). Approximately half (53%) of patients had prior treatment with tafamidis meglumine or diflunisal. Forty-nine percent (49%) and 50% of patients had a New York Heart Association (NYHA) Class of I or II, respectively; patients with NYHA Class III or IV were excluded. The majority of patients (56%) met pre-defined criteria for cardiac involvement, i.e., LV wall thickness ≥ 13 mm at baseline with no history of hypertension or aortic valve disease. Patient demographics and baseline characteristics were balanced between treatment groups, except for a higher proportion of patients in the ONPATTRO group having a non-V30M mutation (62% vs. 48%), and that met pre-defined criteria for cardiac involvement (61% vs. 47%). Ninety-three percent (93%) of ONPATTRO-treated and 62% of placebo-treated patients completed 18 months of the assigned treatment.

The primary efficacy endpoint was the change from baseline to 18 months in the modified Neuropathy Impairment Score +7 (mNIS+7). This endpoint is a composite measure of motor, sensory, and autonomic polyneuropathy including assessments of motor strength and reflexes, quantitative sensory testing, nerve conduction studies, and postural blood pressure, with the score ranging from 0 to 304 points, where an increasing score indicates worsening impairment. The key secondary endpoint was the change from baseline to 18 months in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN questionnaire, a patient-reported score, includes domains relating to small fiber, large fiber, and autonomic nerve function, symptoms of polyneuropathy, and activities of daily living, with the total score ranging from -4 to 136, where increasing score indicates worsening quality of life. Other secondary endpoints measured motor strength (NIS-weakness [NIS-W]), patient-reported ability to perform activities of daily living and social participation such as eating, bathing, dressing, and standing (Rasch-Built Overall Disability Scale [R-ODS]), gait speed (10-meter walk test), nutritional status (modified body mass index [mBMI]), and patient-reported autonomic symptoms such as dizziness, constipation, diarrhea, nausea/vomiting, and incontinence (Composite Autonomic Symptom Score 31 [COMPASS 31]).

13.2 Study Results

Patients treated with ONPATTRO demonstrated significant improvements in the primary endpoint and all secondary endpoints, compared to patients who received placebo (all $p < 0.001$) (Table 5).

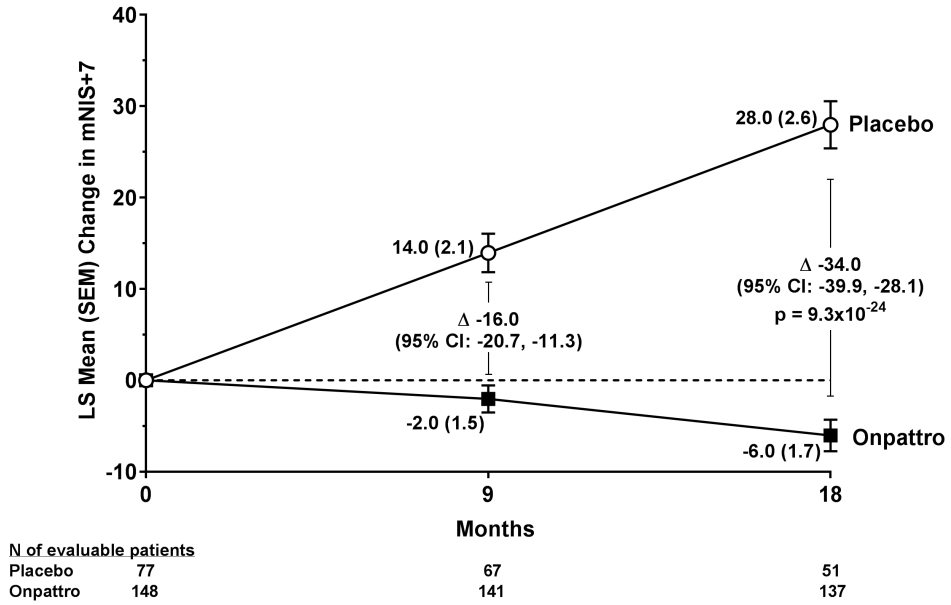
Table 5 - Clinical Efficacy Results from the APOLLO Trial

Endpoint[a]	Baseline, Mean (SD)		Change from Baseline at 18 months, LS Mean (SEM)		ONPATTRO -Placebo Treatment Difference, LS Mean (95% CI)	p-value
	ONPATTRO N=148	Placebo N=77	ONPATTRO	Placebo		
Primary						
mNIS+7[b]	80.9 (41.5)	74.6 (37.0)	-6.0 (1.7)	28.0 (2.6)	-34.0 (-39.9,-28.1)	$9.3x10^{-24}$
Secondary						
Norfolk QoL-DN[b]	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2,-15.0)	$1.1x10^{-10}$
NIS-W[b]	32.7 (25.2)	29.0 (23.0)	0.05 (1.3)	17.9 (2.0)	-17.9 (-22.3,-13.4)	$1.4x10^{-13}$
R-ODS[c]	29.7 (11.5)	29.8 (10.8)	0.0 (0.6)	-8.9 (0.9)	9.0 (7.0, 10.9)	$4.1x10^{-16}$
10-meter walk test (m/sec)[c]	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	$1.9x10^{-12}$
mBMI[d]	970 (210)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	$8.8x10^{-11}$
COMPASS 31[b]	30.6 (17.6)	30.3 (16.4)	-5.3 (1.3)	2.2 (1.9)	-7.5 (-11.9,-3.2)	0.0008

LS mean, least squares mean; SD, standard deviation; SEM, standard error of the mean; CI, confidence interval
[a] All endpoints analyzed using the mixed-effect model repeated measures (MMRM) method.
[b] A lower number indicates less impairment/fewer symptoms
[c] A higher number indicates less disability/less impairment
[d] mBMI: body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status

ONPATTRO treatment led to a 34.0-point improvement in neuropathy (mNIS+7) relative to placebo ($p = 9.3x10^{-24}$), with a mean change from baseline of −6.0 points (improvement) with ONPATTRO compared to an increase of 28.0 points (worsening) with placebo at 18 months (Table 5). Improvement in neuropathy with ONPATTRO relative to placebo was observed at 9 months, the first post-baseline assessment in the study (Figure 1). At 18 months, improvements relative to placebo were observed across all mNIS+7 components, and 56.1% of ONPATTRO-treated patients experienced an improvement in neuropathy (mNIS+7 change from baseline of < 0 points), compared to 3.9% of placebo-treated patients ($p = 1.8x10^{-15}$; odds ratio of 39.9 [95% CI: 11.0, 144.4]). Some patients treated with ONPATTRO had reduced dependence on or no longer required walking aids, which was not observed in placebo-treated patients.

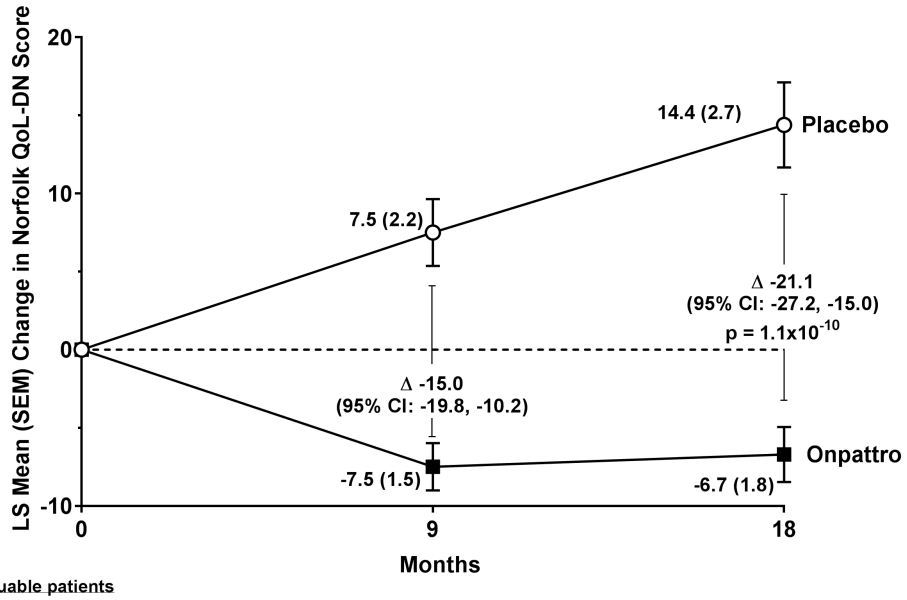
Figure 1: Change from Baseline in mNIS+7



A decrease in mNIS+7 indicates improvement
Treatment difference is shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

ONPATTRO treatment led to a 21.1-point improvement in Norfolk QoL-DN score relative to placebo ($p = 1.1x10^{-10}$), with a mean change from baseline of −6.7 points (improvement) compared to an increase of 14.4 points (worsening) with placebo at 18 months, see Table 5 above. Improvement was observed at 9 months, the first post-baseline assessment in the study (Figure 2). At 18 months, improvements relative to placebo were observed across all domains of Norfolk QoL-DN. 51.4% of ONPATTRO-treated patients experienced an improvement in quality of life (Norfolk QoL-DN change from baseline of < 0 points), compared to 10.4% of placebo-treated patients (odds ratio of 10.0 [95% CI: 4.4, 22.5]).

Figure 2: Change from Baseline in Norfolk QoL-DN Score



N of evaluable patients			
Placebo	76	65	48
Onpattro	148	141	136

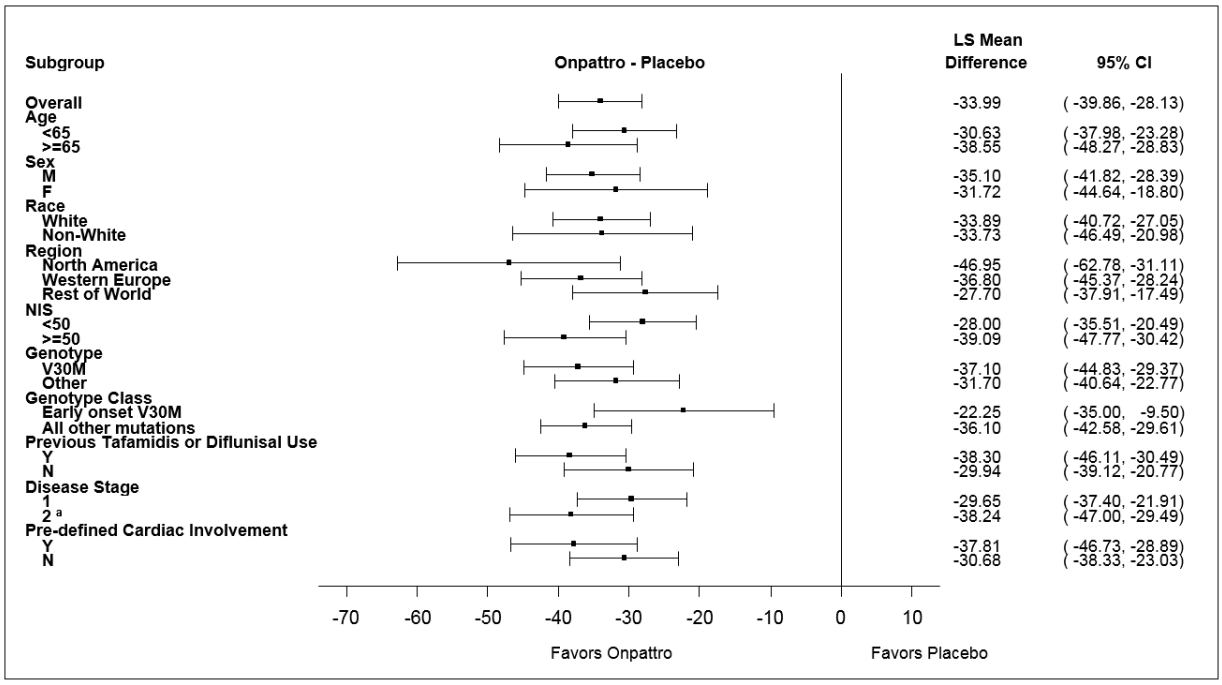
A decrease in Norfolk QoL-DN score indicates improvement.
Treatment difference is shown as the LS mean difference (95% CI) for ONPATTRO – placebo.

ONPATTRO treatment resulted in improvements in motor strength (NIS-W and grip strength), patient-reported ability to perform activities of daily living and social participation (R-ODS) and symptoms of autonomic dysfunction (COMPASS 31), nutritional status (mBMI), as well as faster gait speed (10-meter walk test).

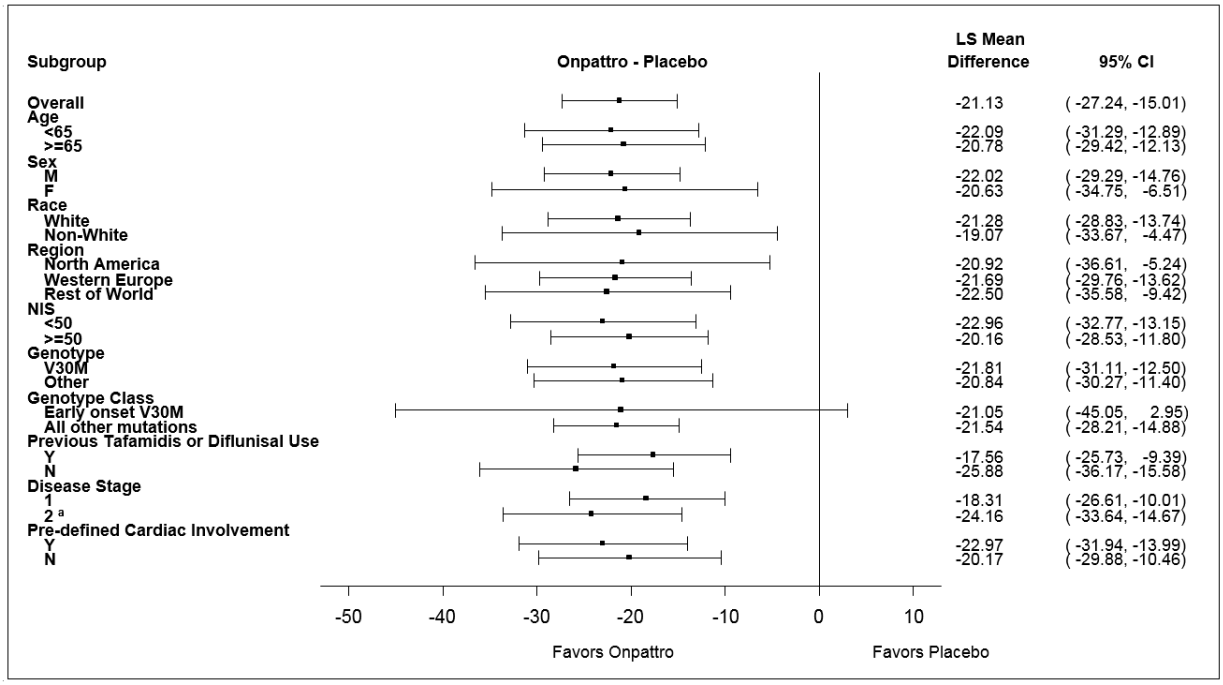
Patients receiving ONPATTRO experienced similar improvements relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, V30M mutation status, prior tafamidis meglumine or diflunisal use, disease stage, and patients that met pre-defined criteria for cardiac involvement (Figure 3).

Figure 3: Forest Plots of Mean Treatment Difference (Change from Baseline to 18 Months), by Subgroup

mNIS+7



Norfolk QoL-DN



[a] 1 patient with stage 3 disease was enrolled in the placebo group prior to implementation of an inclusion criterion that excluded subjects with stage 3 disease; data for this patient was included in the stage 2 disease subgroup in MMRM analyses; this patient did not have a Month 18 mNIS+7 or Norfolk QoL-DN measurement.

In patients with pre-defined cardiac involvement, several cardiac parameters were assessed in the APOLLO study as exploratory endpoints. Centrally assessed echocardiograms showed decreases in LV wall thickness (LS mean difference: −0.9 mm, 95% CI −1.7, −0.2) and absolute longitudinal strain (LS mean difference: −1.37%, 95% CI -2.48, -0.27) from baseline with ONPATTRO treatment, relative to placebo. N-terminal pro-B type natriuretic peptide (NT-proBNP) was 727 ng/L and 711 ng/L (geometric mean) at baseline in ONPATTRO-treated and placebo-treated patients, respectively. NT-proBNP decreased by 11% (95% CI -1%, 22%) in ONPATTRO-treated patients, and increased by 97% (95% CI 55%, 150%) in placebo-treated patients. Improvements in LV wall thickness and NT-proBNP were also observed relative to placebo in the overall study population receiving ONPATTRO.

Data from the APOLLO study was supported by data from two open-label studies that demonstrated maintenance of efficacy for up to 36 months. Furthermore, patients who received placebo in the placebo-controlled study subsequently experienced a mean reduction in mNIS+7 following 12 months of treatment with ONPATTRO in an open-label study.

14 NON-CLINICAL TOXICOLOGY

Patisiran is pharmacologically active in monkeys but not in rodents or rabbits. A rodent-specific surrogate of ONPATTRO, comprised of an siRNA directed against rodent TTR and the same lipid nanoparticle formulation as ONPATTRO, was included in some of the studies in rats.

Animal Pharmacology/Toxicology
Liver and spleen were the primary target organs of toxicity in both rats and monkeys. Intravenous administration of ONPATTRO led to increases in serum liver markers (ALT, AST, ALP, and/or total bilirubin) and histopathology findings in the liver (hepatocellular/single cell necrosis, inflammation, pigment deposition, and/or monocytic infiltration) at doses of > 0.1 mg/kg every 2 or 4 weeks up to 4 doses in rats. Similar microscopic liver findings (minimal to moderate in severity) were observed in monkeys dosed at 3 mg/kg every 2 weeks up to 4 doses; however minimal to moderate increases in ALT, AST and/or LD were observed at ≥ 0.3 mg/kg. In monkeys dosed at 1.0 mg/kg every 3 weeks (14 doses), histopathology findings in liver included centrilobular vacuolation, single cell necrosis, mixed cell infiltration and pigment deposits (all of minimal to slight severity). These changes were not correlated with changes in liver enzymes. At >1.0 mg/kg every 3 weeks (14 doses), these liver findings were of higher severity (minimal, moderate, or marked) and were associated with increases in ALT, AST, and ALP. In spleen, lymphoid atrophy/necrosis and histiocytosis in the white pulp was observed in rats and hypocellularity of the red pulp was observed in monkeys. In general, all findings observed at the end of dosing in the rat and monkey toxicity studies were not observed or were observed with reduced severity at the end of the 60-90 day recovery period, indicating that the toxicities were reversible or partially reversible. The no-observed-adverse-effect level (NOAEL) in rats was 0.1 mg/kg after two doses administered 4 weeks apart (HED < 0.1 times the RHD). The NOAEL in the chronic 9-month monkey toxicity study was 0.3 mg/kg every 3 weeks (HED 0.3 times the RHD).

In monkeys dosed every 3 weeks for 39-weeks, consistent with the pharmacodynamic effect of patisiran, decreases in serum TTR concentrations (up to 98%) were observed. A secondary effect on serum vitamin A concentrations resulted in decreases (up to 81%) that were not associated with signs of vitamin A deficiency, as evaluated through ophthalmic examinations, electroretinograms, and histopathology of the eye. Similarly, a secondary effect on thyroxine (decreases up to 50%) was observed, with no effect on histopathology of the thyroid.

Carcinogenicity
ONPATTRO was not carcinogenic in TgRasH2 mice at doses up to 6 mg/kg every 2 weeks when administered by intravenous bolus for 26 weeks (HED, unadjusted for dosing schedule, 1.7 times the RHD).

Genotoxicity
ONPATTRO was not mutagenic or clastogenic in the Ames bacterial mutagenicity assay, chromosomal aberration assay in human peripheral blood lymphocytes, or in the *in vivo* mouse micronucleus assay.

Teratogenicity
In female rats, intravenous administration of ONPATTRO at doses up to 1.5 mg/kg weekly for 3 weeks prior to mating and on gestation days 6, 13, and 19 did not result in any embryo-fetal defects (HED, unadjusted for dosing schedule, 0.8 times the RHD). Fetal exposure to patisiran and PEG_{2000}-C-DMG (α-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene) was not detectable. Fetal exposure to the lipid component DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate) was negligible (≤ 0.04% of maternal plasma C_{max}).

In pregnant rabbits, intravenous administration of ONPATTRO at doses up to 0.6 mg/kg on gestation days 7, 13, and 19 did not result in any embryo-fetal effects (HED, unadjusted for dosing schedule, 0.6 times the RHD). Spontaneous abortions, reduced embryo-fetal survival, and reduced fetal body weights were observed at doses ≥ 1 mg/kg at doses where maternal toxicity was also observed (HED, unadjusted for dosing schedule, 1.1 times the RHD). There were no external embryo-fetal malformations or variations. Fetal exposure to patisiran was not detectable. Fetal exposure to the lipid components DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate) and PEG_{2000}-C-DMG (α-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene) was negligible (≤ 0.4% of maternal plasma C_{max}).

Intravenous administration of a rodent-specific surrogate to female rats prior to mating and during gestation resulted in the expected pharmacological decreases in circulating TTR concentrations (> 95%) and vitamin A concentrations (88%). No embryo-fetal effects were observed.

Lactation
In female rats administered ONPATTRO or a rodent-specific surrogate at doses up to 1.5 mg/kg on gestation days 7, 13, and 19 and lactation days 6, 12, and 18, there were no effects on mortality, growth, sexual maturation, behavior, mating, fertility, or reproductive performance of the pups (HED, unadjusted for dosing schedule, 0.8 times the RHD). Patisiran was not present in milk, although small amounts of the lipid components DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate) and PEG_{2000}-C-DMG (α-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene) were present in milk (up to 7% of concomitant maternal plasma concentrations).

Impairment of fertility
Intravenous administration of ONPATTRO or a rodent-specific surrogate to male rats at doses up to 0.3 mg/kg every other week (HED, unadjusted for dosing schedule, 0.2 times the RHD) for 10 weeks prior to mating, or to female rats at doses up to 1.5 mg/kg weekly (HED, unadjusted for dosing schedule, 0.8 times the RHD) for 3 weeks prior to mating and on gestation days 6,

13, and 19, had no impact on fertility or reproductive performance. The rat-specific surrogate resulted in the expected pharmacological decreases in serum TTR and vitamin A concentrations, with no impact on fertility or reproductive performance.

Intravenous administration of ONPATTRO at doses up to 2 mg/kg every 3 weeks for 39 weeks (HED 2.2 times the RHD) had no effect on male reproductive assessments in sexually mature cynomolgus monkeys (i.e., semen volume and appearance, sperm concentration, motility, and morphology, testicular size, and spermatogenic staging).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]ONPATTRO™

Patisiran Lipid Complex for Injection

Read this carefully before you start taking ONPATTRO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ONPATTRO.

What is ONPATTRO used for?

ONPATTRO is a medicine that treats an illness which runs in families called hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).
ONPATTRO is used in adults only.

How does ONPATTRO work?

hATTR amyloidosis is caused by problems with a protein in the body called 'transthyretin' (TTR). ONPATTRO works by lowering the amount of TTR protein in the body.
This can help to reduce the symptoms of hATTR amyloidosis.

What are the ingredients in ONPATTRO?

Medicinal ingredient: patisiran

Non-medicinal ingredients: cholesterol, DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate), DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine), PEG_{2000}-C-DMG (α-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene), potassium phosphate monobasic anhydrous, sodium chloride, sodium phosphate dibasic heptahydrate, water for injection

ONPATTRO comes in the following dosage forms:

Lipid complex for injection: 2mg / 1mL.

Do not use ONPATTRO if:

- You have ever had a severe allergic reaction to patisiran, or any of the other ingredients of this medicine. If you are not sure, talk to your doctor or nurse before you are given ONPATTRO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ONPATTRO. Talk about any health conditions or problems you may have.

Other warnings you should know about:

- Infusion-related reactions
  ONPATTRO is given as a drip into a vein (called an 'intravenous infusion'). You may have an infusion-related reaction during treatment with ONPATTRO. To help lower the chance of this, you will be given medicines before each infusion.

  Tell your doctor or nurse right away if you get any signs of an infusion-related reaction. These signs may include:

- Stomach pain
- Nausea
- Body aches or pain, including pain in the back, neck, or joints
- Headache
- Feeling tired
- Chills
- Dizziness
- Cough, feeling short of breath, or other breathing problems
- Reddening of the face or body, warm skin, or rash
- Chest discomfort or chest pain
- Rapid heart rate
- Low or high blood pressure
- Pain, redness, burning sensation, or swelling at or near the infusion site
- Swelling of the face

If you have an infusion-related reaction, your doctor or nurse may slow down or stop your infusion, and you may need to take other medicines. When these reactions stop, or get better, your doctor or nurse may decide to start the infusion again.

- **Lowered vitamin A levels in the blood and vitamin A supplements**
  Treatment with ONPATTRO lowers the amount of vitamin A in your blood. Your doctor will tell you to take a vitamin A supplement every day. Talk to your doctor if you notice a change in your vision.

- **Pregnancy**
  Before starting treatment with ONPATTRO, tell your doctor if you are pregnant, think you may be pregnant, or are planning to have a baby.

  You should not take ONPATTRO if you are pregnant. If you become pregnant while being treated with this medicine, tell your doctor or nurse right away.

- **Breastfeeding**
  Before starting treatment with ONPATTRO, tell your doctor if you are breastfeeding. You and your doctor will decide if the benefit of breastfeeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

- **Birth Control**
  If you are a woman who is able to become pregnant, you should use effective birth control:
  - during treatment with ONPATTRO and
  - for 12 weeks after your last treatment.

  Talk to your doctor or nurse about suitable methods of birth control.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
There are no known relevant drug interactions with ONPATTRO.

How ONPATTRO is given:
- ONPATTRO will be given to you by a doctor or nurse.
- It is given as a drip into a vein ('intravenous infusion') over about 80 minutes.

- You will take other medicines at least 60 minutes before each infusion. They will help to lower the chance that you will have an infusion-related reaction. These medicines include a pain reliever, allergy medicines and a type of steroid (corticosteroid).
- Your doctor will tell you how long you need to receive ONPATTRO. Do not stop treatment with ONPATTRO unless your doctor tells you to.

Usual dose:
- Your doctor will work out how much ONPATTRO to give you – this will depend on your body weight.
- The usual dose of ONPATTRO is 0.3 milligrams (mg) per kilogram (kg) of body weight given once every 3 weeks. The maximum dose is 30mg.

Overdose:
This medicine will be given to you by your doctor or nurse. In the unlikely event that you are given too much (an overdose), your doctor or nurse will check you for side effects

If you think you have been given too much ONPATTRO, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss an appointment to have ONPATTRO, ask your doctor or nurse when to schedule your next treatment.

What are possible side effects from using ONPATTRO?
Like all medicines, ONPATTRO can cause side effects, although not everybody gets them. These are not all the possible side effects you may feel when taking ONPATTRO. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Pain in the joints
- Muscle spasms
- Indigestion
- Redness of the skin
- Stuffy or runny nose
- Irritation or infection of the airways

Serious side effects and what to do about them			Stop taking drug and get immediate medical help
Symptom / effect	Talk to your healthcare professional		
	Only if severe	In all cases	
VERY COMMON			
Swelling of the arms or legs (peripheral edema)	√		
Infusion-related reaction	√		
COMMON			
Shortness of breath	√		
Feeling dizzy or faint (vertigo)	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in a refrigerator (2°C to 8°C). Do not freeze.
- If refrigeration is not available, ONPATTRO can be stored at room temperature (up to 25°C for up to 14 days).
- Do not use this medicine after the expiration date, which is stated on the carton after 'EXP'. The expiration date refers to the last day of that month.
- Keep out of reach and sight of children.
- Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

If you want more information about ONPATTRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (Alnylam.ca/onpattro-monograph-en; Alnylam.ca/onpattro-monograph-fr) or by calling 1-877-256-9526.

This leaflet was prepared by Alnylam Netherlands B.V.

Last Revised June 7, 2019