▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ONPATTRO® (patisiran)

1. NAME OF THE MEDICINE

Patisiran

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains patisiran sodium equivalent to 2 mg patisiran.

Each vial contains patisiran sodium equivalent to 10 mg patisiran formulated as lipid nanoparticles.

Excipients with known effect

Each mL of concentrate contains 3.99 mg sodium.

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Concentrated injection for infusion (sterile concentrate).

White to off-white, opalescent, homogeneous solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis.

Dosage
The recommended dose of Onpattro is 300 micrograms per kg body weight administered via intravenous (IV) infusion once every 3 weeks.

Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg.
Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised for patients treated with Onpattro (see section 4.4 Special Warnings and Precautions for Use).

Required premedication
All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs) (see section 4.4 Special Warnings and Precautions for Use). Each of the following medicinal products 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 paracetamol (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 in decrements no greater than 2.5 mg to a minimum dose of 5 mg of dexamethasone (IV), or equivalent. The patient should receive at least 3 consecutive IV infusions of Onpattro without experiencing IRRs before each reduction in corticosteroid premedication.

Additional or higher doses of one or more of the premedications may be administered to reduce the risk of IRRs, if needed (see sections 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable Effects)).

Missed dose
If a dose is missed, Onpattro should be administered as soon as possible.

- If Onpattro is administered within 3 days of the missed dose, dosing should be continued according to the patient's original schedule.
- If Onpattro is administered more than 3 days after the missed dose, dosing should be continued every 3 weeks thereafter.

Special populations

Elderly patients
No dose adjustment is required in patients ≥ 65 years of age (see section 5.2 Pharmacokinetic Properties).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤ 1 x ULN and AST > 1 x ULN, or bilirubin > 1.0 to 1.5 x ULN and any AST; see section 5.2 Pharmacokinetic Properties).

Liver transplant
Onpattro has not been studied in patients with prior liver transplant; however, no dose adjustments are considered necessary.

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 section 5.2 Pharmacokinetic Properties).

Paediatric population
The safety and efficacy of Onpattro in children or adolescents < 18 years of age have not been established. No data are available.

Method of administration

Onpattro is for intravenous use. It is for single use only.

Dilution
Onpattro must be diluted with sodium chloride 9 mg/mL (0.9%) solution 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.
- Discard vial if it has been frozen.
- Inspect visually for particulate matter and discolouration. Do not use if discolouration 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 (see section 4.2 Dose and Method of Administration).
- 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 sodium chloride 9 mg/mL (0.9%) solution for a total volume of 200 mL. Use infusion bags that are free of di(2-ethylhexyl)phthalate (DEHP).
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other medicinal products.
- Discard any unused portion of Onpattro. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Infusion process

- A dedicated line with an infusion set containing a 1.2 micron polyethersulfone (PES) in-line infusion filter must be used. The infusion sets and lines must be free of di(2-ethylhexyl)phthalate (DEHP).
- The diluted solution of Onpattro should be infused intravenously over approximately 80 minutes at an initial infusion rate of approximately 1 mL/min for the first 15 minutes, followed by an 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 section 4.4 Special Warnings and Precautions for Use).

- Onpattro must be administered through a free-flowing venous access line. The infusion site should be monitored for possible infiltration during administration. Suspected extravasation should be managed according to local standard practice for non-vesicants.
- The patient should be observed during the infusion and, if clinically indicated, following the infusion (see section 4.4 Special Warnings and Precautions for Use).
- After completion of the infusion, the intravenous administration set should be flushed with sodium chloride 9 mg/mL (0.9 %) solution to ensure that all medicinal product has been administered.

Infusion of Onpattro at home may be considered for patients who have tolerated at least 3 infusions well in the clinic. The decision for a patient to receive home infusions should be made after evaluation and recommendation by the treating physician. Home infusions should be performed by a healthcare professional.

4.3 CONTRAINDICATIONS

Severe hypersensitivity (e.g., anaphylaxis) to the active substance or any of the excipients listed in section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infusion-related reactions

IRRs have been observed in patients treated with Onpattro. In patients experiencing an IRR, the majority experienced the first IRR within the first 2 infusions (see section 4.8 Adverse Effects (Undesirable Effects)). Across clinical studies, the most common symptoms (reported in ≥ 2% of patients) of IRRs were flushing, back pain, nausea, abdominal pain, dyspnoea, and headache. IRRs may also include hypotension and syncope.

To reduce the risk of IRRs, patients should receive premedications on the day of Onpattro infusion, at least 60 minutes prior to the start of infusion (see section 4.2 Dose and Method of Administration). If an IRR occurs, slowing or interrupting the infusion and institution of medical management (e.g., corticosteroids or other symptomatic treatment) should be considered, as clinically indicated. If the infusion is interrupted, resumption of the infusion at a slower infusion rate may be considered after symptoms have resolved. The Onpattro infusion should be discontinued 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.

Vitamin A deficiency

By reducing serum TTR protein, Onpattro treatment leads to a decrease in serum vitamin A (retinol) levels (see section 5.1 Pharmacodynamic Properties). Serum vitamin A levels below the lower limit of normal should be corrected and any ocular symptoms or signs due to vitamin A deficiency should be evaluated prior to initiation of treatment with Onpattro.

Patients receiving Onpattro should take oral supplementation of approximately 2500 IU vitamin A per day to reduce the potential risk of ocular toxicity due to vitamin A deficiency. Referral for ophthalmological assessment is recommended if patients develop ocular symptoms suggestive of vitamin A deficiency, including reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening or corneal perforation.

Serum vitamin A levels should not be used to guide vitamin A supplementation during treatment with Onpattro.

During the first 60 days of pregnancy, both too high or too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should be excluded before initiating Onpattro and women of childbearing potential should practise effective contraception. If a woman intends to become pregnant, Onpattro and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted.

In the event of an unplanned pregnancy, Onpattro should be discontinued (see section 4.6 Fertility, Pregnancy and Lactation). Vitamin A supplementation should be discontinued during the first trimester, unless the pregnant woman has clinical signs of vitamin A deficiency. If such signs are present, vitamin A supplementation should not exceed 2500 IU per day. Thereafter, vitamin A supplementation of 2500 IU per day should be resumed in the second and third trimesters if serum vitamin A levels have not returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

Use in hepatic impairment

Onpattro has not been studied in patients with moderate or severe hepatic impairment and should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk (see section 5.2 Pharmacokinetic Properties).

Use in renal impairment

Onpattro has not been studied in patients with severe renal impairment or end-stage renal disease and should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk (see section 5.2 Pharmacokinetic Properties).

Use in the elderly

There are no special precautions for the use of Onpattro in the elderly.

Paediatric use

The safety and efficacy of Onpattro in children or adolescents < 18 years of age have not been established. No data are available.

Effects on laboratory tests

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, during treatment with Onpattro, 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 (see sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

Excipients

This medicinal product contains 3.99 mg sodium per mL, equivalent to 0.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal clinical drug interaction studies have been performed. The pharmacokinetics of Onpattro components are not expected to be affected by inhibitors or inducers of cytochrome P450 enzymes or to cause drug-drug interactions, except for induction and time-dependent inhibition of CYP2B6 *in vitro*. The net effect on CYP2B6 substrates (e.g., bupropion and efavirenz) *in vivo* is unknown.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no data on the effects of Onpattro on human fertility.

Intravenous (IV) administration of patisiran-LNP (lipid nanoparticle) (up to 0.3 mg/kg) or a rodent-specific (pharmacologically active) surrogate (0.1 mg/kg) to male rats every two weeks prior to and throughout mating to untreated females produced no adverse effects on fertility. Maximum exposures to the components of the test items were subclinical.

Intravenous administration of patisiran-LNP (up to 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility. Maximum exposures to the components of the test items were similar to or marginally above clinical exposures at the maximum recommended human dose (MRHD).

Intravenous administration of patisiran-LNP (up to 2 mg/kg) to adult monkeys every three weeks for 39 weeks produced no adverse effects on male reproductive organs or on sperm morphology or count. Maximum exposures were similar to clinical exposures to patisiran at the MRHD. Maximum exposures to the lipid components were 7 to 9 times the clinical exposures to these components at the MRHD.

Use in Pregnancy – Category D

Pregnancy
There are no data on the use of Onpattro in pregnant women.

Onpattro treatment leads to a decrease in serum vitamin A levels. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects.

Animal studies are insufficient with respect to developmental toxicity. Intravenous administration of patisiran-LNP (up to 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on embryofetal development. Maximum exposures to the components of the test items were subclinical.

Intravenous administration of patisiran-LNP (up to 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. Maximum exposure to the components of the test items were subclinical. In a separate study, patisiran-LNP (up to 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at doses ≥1 mg/kg, which were associated with maternal toxicity.

Intravenous administration of patisiran-LNP (up to 1.5 mg/kg) or a rodent-specific surrogate (1.5 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Maximum exposures to the components of the test items were subclinical or similar to clinical exposures at the MRHD in the above animal studies.

Women of childbearing potential
Treatment with Onpattro reduces serum levels of vitamin A. Both too high or too low vitamin A levels may be associated with an increased risk of fetal malformation. Therefore, pregnancy should be excluded before initiation of treatment and women of childbearing potential should use effective contraception. If a woman intends to become pregnant, Onpattro and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted.

Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Onpattro should not be used during pregnancy, unless the clinical condition of the woman requires treatment. As a precautionary measure, vitamin A and thyroid stimulating hormone (TSH) levels should be obtained early in pregnancy. Close monitoring of the fetus should be carried out in the event of an unplanned pregnancy, especially during the first trimester (see section 4.4 Special Warnings and Precautions for Use). Women of childbearing potential have to use effective contraception during treatment with Onpattro.

Use in lactation

No studies have been conducted to assess the presence of components of Onpattro in human milk, the effects on the breastfed child or the effects on milk production. 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 (up to 7 % of concomitant maternal plasma concentrations). There were no adverse effects on the pups.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Onpattro, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

On the basis of the pharmacodynamic and pharmacokinetic profiles, Onpattro is considered to have no or negligible influence on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most frequently occurring adverse reactions reported in Onpattro-treated patients in clinical trials were peripheral oedema (29.7%) and infusion-related reactions (18.9%). The only adverse reaction resulting in the discontinuation of Onpattro was an infusion-related reaction (0.7%).

Tabulated list of adverse reactions

The adverse reactions are presented as MedDRA preferred terms under the MedDRA System Organ Class (SOC) by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency of the adverse reactions is expressed according to the following categories:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)

Table 1: Adverse reactions reported for Onpattro 300 micrograms per kg

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Bronchitis	Common
	Sinusitis	Common
	Rhinitis	Common
Immune system disorders	Infusion-related reaction	Very common
Ear and labyrinth disorders	Vertigo	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Erythema	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Muscle spasms	Common
General disorders and administration site conditions	Peripheral oedema	Very common
	Extravasation	Uncommon

Description of selected adverse reactions

Infusion-related reactions
Symptoms of IRRs 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, dyspnoea or cough, chest discomfort or chest pain, headache, rash, pruritus, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension which may include syncope, hypertension, facial oedema.

In clinical studies, all patients received premedication with a corticosteroid, paracetamol, and H1 and H2 blockers to reduce the risk of IRRs. In the double-blind placebo-controlled study, 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. For clinical management of IRRs, see section 4.4. Special Warning and Precautions for Use.

Peripheral oedema
In the placebo-controlled study, peripheral oedema was reported in 29.7% of Onpattro-treated patients and 22.1% of placebo-treated patients. All events were mild or moderate in severity and did not lead to treatment discontinuation. In Onpattro-treated patients, the events decreased in frequency over time.

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 during treatment with Onpattro. One additional patient had pre-existing anti-drug antibodies. Anti-drug antibody titres were low and transient with no evidence of an effect on clinical efficacy, the safety profile, or the pharmacokinetic or pharmacodynamic profiles of Onpattro.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and given symptomatic treatment, as appropriate.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other nervous System Drugs; ATC code: N07XX12.

Mechanism of action

Onpattro contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA) that targets a genetically conserved sequence in the 3’ untranslated region of a number of variant

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 process called RNA interference (RNAi), patisiran causes the catalytic degradation of *TTR* mRNA in the liver, resulting in a reduction of serum TTR protein.

Pharmacodynamic effects

Mean serum TTR was reduced by approximately 80% within 10 to 14 days after a single dose with 300 micrograms per kg Onpattro. With repeat dosing every 3 weeks, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 84%, respectively. Serum TTR reduction was maintained with continued dosing.

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 section 4.4 Special Warnings and Precautions for Use).

Clinical trials

The efficacy of Onpattro was studied in a randomised, double-blind, placebo-controlled study in 225 hATTR amyloidosis patients with a TTR variant and symptomatic polyneuropathy. Patients were randomised 2:1 to receive 300 micrograms per kg Onpattro or placebo via intravenous infusion once every 3 weeks for 18 months. All patients received premedication with a corticosteroid, paracetamol, and H1 and H2 blockers.

In the study, 148 patients received Onpattro and 77 patients received placebo. The median patient age at baseline was 62 (range 24 to 83) years and 74% of patients were male, 26% were female. Thirty-nine (39) different TTR variants 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 variant and early onset of symptoms (< 50 years of age). 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. Approximately half of patients (56%) met pre-defined criteria for cardiac involvement (defined as baseline LV wall thickness ≥ 13 mm with no history of hypertension or aortic valve disease). Patient demographics and baseline characteristics were balanced between treatment groups, except that a higher proportion of patients in the Onpattro group had a non-V30M variant (62% vs. 48%). 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 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.

A statistically significant benefit in mNIS+7 with Onpattro relative to placebo was observed at 18 months (Table 2). Benefits relative to placebo were also observed across all mNIS+7 components. Changes were also seen at 9 months, the first post-baseline assessment in the study, where treatment with Onpattro led to a 16.0-point treatment difference, with a mean change from baseline of -2.0 points, compared to an increase of 14.0 points with placebo. In a threshold analysis of mNIS+7 (change from baseline of < 0 points), 56.1% of Onpattro-treated patients versus 3.9% of placebo-treated patients experienced improvement in mNIS+7 (p <0.001).

Patients treated with Onpattro experienced statistically significant benefits in all secondary endpoints compared to patients who received placebo (all p <0.001) (Table 2).

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 (patient-reported) includes domains relating to small fibre, large fibre, and autonomic nerve function, symptoms, and activities of daily living, with the total score ranging from -4 to 136, where an increasing score indicates worsening quality of life. At 18 months, a benefit with Onpattro compared to placebo was observed across all domains of Norfolk QoL-DN, and 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. Improvement was observed at 9 months, the first post-baseline assessment in the study.

Table 2: Clinical Efficacy Results from the Placebo-Controlled Study

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)	p < 0.001
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)	p < 0.001
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)	p < 0.001
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)	p < 0.001
10-metre 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)	p < 0.001
mBMI[d]	970 (210)	990 (214)	−3.7 (9.6)	−119 (14.5)	116 (82, 149)	p < 0.001

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		
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)	p < 0.00 1

SD, standard deviation; LS mean, least squares mean; SEM, standard error of the mean; CI, confidence interval, NIS-W, NIS-weakness (motor strength); R-ODS, Rasch-Built Overall Disability (patient reported ability to perform activities of daily living); 10-metre walk test (gait speed); mBMI, modified body mass index (nutritional status); COMPASS 31, Composite Autonomic Symptom Score 31 (patient reported symptom score)

[a]All endpoints analysed 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.
dmBMI: body mass index (BMI; kg/m2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status; nutritional status favoured Onpattro as early as 3 months.

Patients receiving Onpattro experienced similar benefits relative to placebo in mNIS+7 and Norfolk QoL-DN score across all subgroups including age, sex, race, region, NIS score, V30M variant status, prior tafamidis meglumine or diflunisal use, disease stage, and patients with pre-defined cardiac involvement. Patients experienced benefit across all TTR variants and the full range of disease severity studied.

In patients with pre-defined cardiac involvement, centrally-assessed echocardiograms showed decreases in LV wall thickness (LS mean difference: −0.9 mm [95% CI −1.7, −0.2]) and longitudinal strain (LS mean difference: −1.37% [95% CI -2.48, -0.27]) with Onpattro treatment relative to placebo. N-terminal pro-B type natriuretic peptide (NT-proBNP) was 727 ng/L and 711 ng/L at baseline (geometric mean) in Onpattro-treated and placebo-treated patients, respectively. At 18 months, the adjusted geometric mean ratio to baseline was 0.89 with Onpattro and 1.97 with placebo (ratio, 0.45; p < 0.001), representing a 55% difference in favour of Onpattro.

5.2 PHARMACOKINETIC PROPERTIES

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.

Absorption

Greater than 95% of patisiran in the circulation is associated with lipid nanoparticles. At the dose regimen of 300 micrograms per kg every 3 weeks, steady state was reached by 24 weeks of treatment. The estimated patisiran mean ± SD steady-state peak concentration (C_{max}), trough concentration (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.

The estimated DLin-MC3-DMA mean ± SD steady-state $C_{max,}$ C_{trough} and AUC_{τ} were 40.2 ± 11.5 µg/mL, 1.75 ± 0.698 µg/mL, and 1403 ± 105 µg·h/mL, respectively. The accumulation of AUC_{τ} was 1.76-fold at steady-state compared to the first dose.

The estimated PEG_{2000}-C-DMG mean ± SD steady-state $C_{max,}$ C_{trough} and AUC_{τ} were 4.22 ± 1.22 µg/mL, 0.0236 ± 0.0093 µg/mL, and 145 ± 64.7 µg·h/mL, respectively. There was no accumulation of AUC_{τ} at steady-state compared to the first dose.

Distribution

Plasma protein binding of Onpattro is low, with ≤ 2.1% binding observed *in vitro* with human serum albumin and human α1-acid glycoprotein. At the dose regimen of 300 micrograms per kg every 3 weeks, the mean ± SD steady-state volume of distribution (V_{ss}) of patisiran, DLin-MC3-DMA and PEG_{2000}-C-DMG was 0.26 ± 0.20 L/kg, 0.47 ± 0.24 L/kg and 0.13 ± 0.05 L/kg, respectively.

Metabolism

Patisiran is metabolised by nucleases to nucleotides of various lengths. DLin-MC3-DMA is primarily metabolised to 4-dimethylaminobutyric acid (DMBA) by hydrolysis. There is little to no metabolism of PEG_{2000}-C-DMG.

Excretion

At the dose regimen of 300 micrograms per 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 ($t_{1/2\beta}$) of patisiran 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.

Linearity/non-linearity

Exposure to patisiran and the lipid components (DLin-MC3-DMA and PEG_{2000}-C-DMG) increased proportionally with increase in dose over the range evaluated in clinical studies (10 to 500 micrograms per kg). Patisiran and the lipid components exhibit linear and time-independent pharmacokinetics with chronic dosing at the dose regimen of 300 micrograms per kg every 3 weeks.

Pharmacokinetic/pharmacodynamic relationship(s)

Increasing the dose of patisiran resulted in greater TTR reduction, with maximal reductions plateauing at patisiran exposures obtained with 300 micrograms per kg every 3 weeks dosing.

Interactions

The components of Onpattro are not inhibitors or inducers of cytochrome P450 enzymes or transporters, except for CYP2B6 (see Section 4.5 Interactions with other Medicines and other Forms of Interactions). Patisiran is not a substrate of cytochrome P450 enzymes.

Special populations

Gender and race
Clinical studies did not identify significant differences in steady state pharmacokinetic parameters or TTR reduction according to gender or race (non-Caucasian vs. Caucasian).

Weight
No data are available for patients weighing ≥ 110 kg.

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

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.

5.3 PRECLINICAL SAFETY DATA

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.

Carcinogenicity

Onpattro was not carcinogenic in transgenic rasH2 mice at doses up to 6 mg/kg every 2 weeks when administered by intravenous bolus for 26 weeks (≤3-fold the human systemic exposure to Onpattro components at the clinically recommended dose).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino) butanoate)
PEG_{2000}-C-DMG (1,2-Dimyristoyl-sn-glycero-3-carboxaminopropylpolyethylene glycol 2000 methyl ether)
Distearoylphosphatidylcholine [DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)]
Cholesterol
Dibasic sodium phosphate heptahydrate
Monobasic potassium phosphate
Sodium chloride
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Special Precautions for Disposal.

6.3 SHELF LIFE

Unopened vials

36 months.

After dilution
To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If not used immediately and if storage is necessary, hold at room temperature (15°C up to 30°C) for up to 16 hours (including infusion time). Do not freeze.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C. (Refrigerate. Do not freeze).

If refrigeration is not available, Onpattro vials can be stored at room temperature up to 25°C for up to 14 days. Onpattro must be discarded if not used within the 14 day period.

For storage conditions after dilution of the medicinal product, see section 6.3. Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

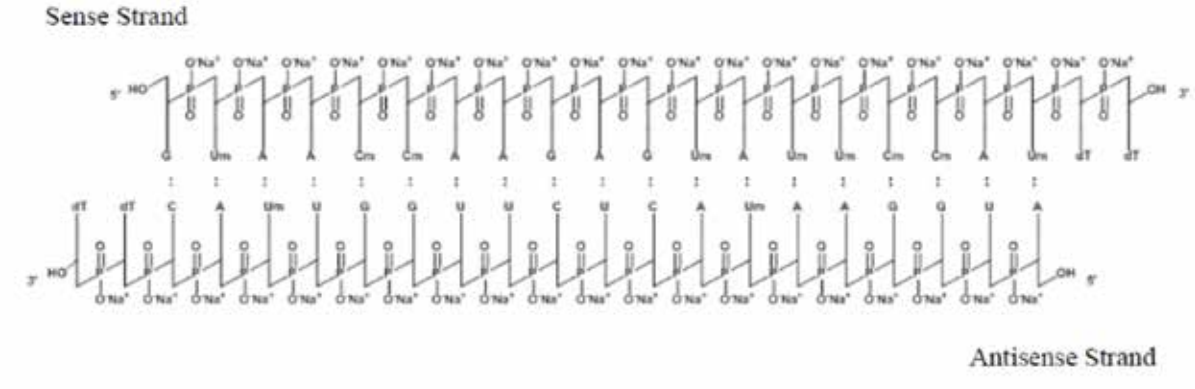
5 mL concentrate in a Type I glass vial with a chlorobutyl stopper and an aluminium flip-off cap. Pack size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1386913-72-9 (patisiran sodium)

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Alnylam Australia Pty Ltd
Level 1,
60 Martin Place,
Sydney
NSW 2000
Australia

9. DATE OF FIRST APPROVAL

21 November 2022

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information