ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onpattro 2 mg/mL concentrate for solution for infusion

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.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

White to off-white, opalescent, homogeneous solution (pH approximately 7).

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 Posology and method of administration

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

Posology

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.

Treatment should be initiated as early as possible after symptom onset (see section 5.1). The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment (see section 5.1).

Vitamin A supplementation at approximately 2 500 IU vitamin A per day is advised for patients treated with Onpattro (see section 4.4).

Required premedication

All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs) (see section 4.4). 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 and 4.8).

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).

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤ 1 x upper limit of normal [ULN] and aspartate aminotransferase [AST] > 1 x ULN, or bilirubin > 1.0 to 1.5 x ULN and any AST). 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).

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). 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).

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.

- Onpattro must be diluted prior to intravenous infusion (see section 6.6).

- 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).
- 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).
- 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.

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). 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). 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 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). 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.

Patients receiving Onpattro should take oral supplementation of approximately 2 500 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 (see section 4.5).

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). 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 2 500 IU per day. Thereafter, vitamin A supplementation of 2 500 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.

Excipients with known effect

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 medicinal products and other forms of interaction

No formal clinical drug interaction studies have been performed. At doses higher than the clinically relevant dose, induction and time-dependent inhibition of CYP2B6 was observed in vitro. The net effect on CYP2B6 substrates (e.g., bupropion and efavirenz) in vivo is unknown.
Onpattro is not expected to cause interactions or be affected by inhibitors or inducers of cytochrome P450 enzymes.

Vitamin A testing

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 and 5.1).

4.6 Fertility, pregnancy and lactation

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 foetal 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.

Pregnancy

There are no data on the use of Onpattro in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). 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 (see section 5.3). Close monitoring of the foetus should be carried out in the event of an unplanned pregnancy, especially during the first trimester (see section 4.4). Women of childbearing potential have to use effective contraception during treatment with Onpattro.

Breast-feeding

It is unknown whether Onpattro is excreted in human milk. A risk to the breastfed newborn/infant cannot be excluded. Available toxicological data in animals have shown excretion of small amounts of the lipid components DLin-MC3-DMA and PEG_{2000}-C-DMG in milk (see section 5.3).

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.

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 section 5.3).

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 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions reported in Onpattro-treated patients were peripheral oedema (29.7%) and infusion-related reactions (18.9%). One patient (0.7%) discontinued treatment during clinical studies due to an infusion-related reaction.

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, dysphonia, 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. Some patients still experienced IRRs after 18 months of treatment, and in a few patients IRRs continued to be frequent. 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.

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.

Other special population(s)

Liver transplant recipients

In an open-label study in 23 hATTR amyloidosis patients with polyneuropathy progression post liver transplant, the safety profile of patisiran was consistent with previous clinical studies (see section 5.1).

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 reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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.

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 specifically targets a genetically conserved sequence in the 3' untranslated region of all 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 natural 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 sections 4.4 and 4.5).

Clinical efficacy

The efficacy of Onpattro was studied in a randomised, double-blind, placebo-controlled study in 225 hATTR amyloidosis patients with a TTR mutation 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 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 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 left ventricular [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 mutation (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 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
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 < 0.001

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.
[d]mBMI: body mass index (BMI; kg/m^2) 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 mutation status, prior tafamidis meglumine or diflunisal use, disease stage, and patients with pre-defined cardiac involvement. Patients experienced benefit across all TTR mutations 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.

Global open-label extension study

Of 218 patients who completed one of the two parent studies with patisiran (18-month placebo-controlled study [Study 004] or 2-year open-label study [Study 003]), 211 patients (25 prior patisiran from Study 003, 49 prior placebo and 137 prior patisiran from Study 004) enrolled in a global open-label extension study (Study 006). All patients in Study 006 received 300 micrograms per kg of

patisiran via IV infusion once every 3 weeks. At Study 006 baseline, for the prior (Study 004) patisiran and placebo groups, 42.3% and 28.6% had stage 1 disease, 51.8% and 55.1% had stage 2 disease and 5.8% and 16.3% had stage 3 disease, respectively.

After initiation of patisiran in Study 006, clinical benefit was observed in patients who previously received placebo as demonstrated by stable measures of disease manifestations. Although these patients achieved stabilisation of their disease, measures of disease manifestations remained worse compared to the prior patisiran group, supporting the early initiation of patisiran treatment after the onset of symptoms. Continued treatment with patisiran through Year 3, across a range of disease stages, resulted in continued benefit.

Liver transplant recipients

In an open-label study, 23 patients with hATTR amyloidosis and polyneuropathy progression after receiving a liver transplant were treated with patisiran at a dose of 300 micrograms per kg via IV infusion once every 3 weeks. Median time from transplant to first patisiran dose was 9.4 years and median duration of patisiran treatment was 13.1 months. All patients received concomitant immunosuppressants. The study demonstrated a statistically significant median reduction in serum TTR levels from baseline of 91% ($p < 0.001$). Patients also showed stable or improved efficacy endpoints at Month 12 compared to baseline. This was consistent with the findings in the placebo-controlled patisiran study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Onpattro in all subsets of the paediatric population in hATTR amyloidosis (see section 4.2 for information on paediatric use).

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.

Biotransformation

Patisiran is metabolized 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.

Elimination

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). 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.

Liver transplant

In a clinical study in hATTR amyloidosis patients who had undergone prior liver transplant, steady state pharmacokinetic parameters and TTR reduction were comparable to those observed in patients without a liver transplant.

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

General 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 (alanine aminotransferase [ALT], AST, alkaline phosphatase [ALP], and/or total bilirubin) and histopathology findings in the liver (hepatocellular/single cell necrosis, inflammation, pigment deposition, and/or monocytic infiltration) at doses > 100 micrograms per kg every 4 weeks and > 1.0 mg/kg every 3 weeks in rats and monkeys, respectively. 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 had either a full recovery or were observed with reduced severity at the end of the 60-90 day recovery period, indicating at least partial reversibility.

Genotoxicity/Carcinogenicity

Onpattro did not exhibit a genotoxic potential in vitro and in vivo and was not carcinogenic in transgenic rasH2 mice.

Reproductive toxicity

In rats, while there were parental decreases in serum TTR (≥ 90%), thyroxine (≥ 66%) and vitamin A (≥ 75%) levels using a rat specific surrogate to patisiran, no effects were found on male or female fertility, embryo-foetal development, or pre-/post-natal development.

In rabbits, Onpattro generated spontaneous abortions, reduced embryo-foetal survival, and reduced foetal body weights at maternally toxic doses ≥ 1 mg/kg (human equivalent dose [HED] 3.2 times the recommended human dose [RHD]). As patisiran is not pharmacologically active in rabbits, these effects are not due to reductions in TTR, thyroxine or vitamin A.

Intravenous administration of Onpattro had no effect on male reproductive assessments in sexually mature cynomolgus monkeys.

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 (up to 7% of concomitant maternal plasma concentrations). There were no adverse effects on the pups.

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 (α-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene)
DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine)
Cholesterol
Disodium hydrogen phosphate, heptahydrate
Potassium dihydrogen phosphate, anhydrous
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.

6.3 Shelf life

Unopened vials

3 years.

After dilution

Chemical and physical in-use stability has been demonstrated for 16 hours at room temperature (up to 30°C). From a microbiological point of view, it is recommended that the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 16 hours at either 2°C to 8°C or room temperature (up to 30°C), including infusion time.

6.4 Special precautions for 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.

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

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).
- 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.

7. MARKETING AUTHORISATION HOLDER

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1320/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 August 2018
Date of latest renewal: 04 April 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Onpattro in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where Onpattro is marketed, all health care professionals (HCPs) and patients are provided with educational materials in order to ensure the safe and sustainable administration of the product in the home setting, aiming at preventing and/or minimising the important identified risk of Infusion Related Reactions (IRRs).

- The educational material for HCPs should include information about:
- Suitability of the patient for home infusion;

- Requirements for home infusion, including availability and timely administration of the appropriate premedication;
- The appropriate infusion rate;
- Signs and symptoms of IRRs;
- Action to take in the event of an IRRs and in case of emergency;
- Steps to consider to prevent further IRRs;
- Reasons triggering HCPs to consider whether the patient should stop home infusions and return to the clinic to receive the infusions.

The educational material for patients (a home infusion guide detailing the steps to undertake during home infusion) should include information about:

- How the infusion is given;
- The potential for IRRs to occur;
- Signs and symptoms of IRRs;
- Patients to inform immediately the HCP if they experience any of the signs and symptoms of IRRs.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Onpattro 2 mg/mL concentrate for solution for infusion
patisiran

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains patisiran sodium equivalent to 2 mg patisiran.

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

3. LIST OF EXCIPIENTS

Excipients

DLin-MC3-DMA
PEG_{2000}-C-DMG
DSPC
Cholesterol
Disodium hydrogen phosphate, heptahydrate
Potassium dihydrogen phosphate, anhydrous
Sodium chloride
Water for injections

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
10 mg/5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not shake or vortex.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1320/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onpattro

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Onpattro 2 mg/mL sterile concentrate
patisiran
IV use after dilution

2. METHOD OF ADMINISTRATION

Do not shake or vortex.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Onpattro 2 mg/mL concentrate for solution for infusion
patisiran

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Onpattro is and what it is used for

The active substance in Onpattro is patisiran.

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

hATTR amyloidosis is caused by problems with a protein in the body called 'transthyretin' (TTR).
- This protein is made mostly in the liver and carries vitamin A and other substances around the body.
- In people with this illness, abnormally shaped TTR proteins clump together to make deposits called 'amyloid'.
- Amyloid can build up around the nerves, heart, and other places in the body, preventing them from working normally. This causes the symptoms of the illness.

Onpattro works by lowering the amount of TTR protein that the liver makes.
- This means there is less TTR protein in the blood that can form amyloid.
- This can help to reduce the effects of this illness.

Onpattro is used in adults only.

2. What you need to know before you are given Onpattro

You must not be given Onpattro

- if you have ever had a severe allergic reaction to patisiran, or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or nurse before you are given Onpattro.

Warnings and precautions

Infusion-related reactions

Onpattro is given as a drip into a vein (called an 'intravenous infusion'). Reactions to this infusion may happen during treatment with Onpattro. Before each infusion you will be given medicines that help to lower the chance of infusion-related reactions (see "Medicines given during treatment with Onpattro" in section 3).

Tell your doctor or nurse straight away if you get any signs of an infusion-related reaction. These signs are listed at the beginning of section 4.

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 to control the symptoms. When these reactions stop, or get better, your doctor or nurse may decide to start the infusion again.

Vitamin A deficiency

Treatment with Onpattro lowers the amount of vitamin A in your blood. Your doctor will measure your vitamin A levels. If your vitamin A levels are low, your doctor will wait until your vitamin A levels have returned to normal and any symptoms due to vitamin A deficiency have resolved before you start treatment with Onpattro.. Symptoms of vitamin A deficiency may include:

- Decrease in night vision, dry eyes, poor vision, hazy or cloudy vision

If you have problems with your vision or any other eye problems whilst using Onpattro, you should talk to your doctor. Your doctor may refer you to an eye specialist for a check-up if it is necessary.

Your doctor will ask you to take a daily vitamin A supplement during treatment with Onpattro.

Both too high and too low levels of vitamin A can harm the development of your unborn child. Therefore, women of child-bearing age should not be pregnant when starting treatment with Onpattro and should practise effective contraception (see section "Pregnancy, breast-feeding and contraception" below).

Tell your doctor if you are planning to become pregnant. Your doctor may tell you to stop taking Onpattro. Your doctor will ensure that your vitamin A levels have returned to normal before you try to become pregnant.

Tell your doctor if you have an unplanned pregnancy. Your doctor may tell you to stop taking Onpattro. During the first 3 months of your pregnancy, your doctor may tell you to stop your vitamin A supplement. During the last 6 months of your pregnancy you should resume vitamin A supplementation if the vitamin A levels in your blood have not yet returned to normal, because of an increased risk of vitamin A deficiency during the last 3 months of your pregnancy.

Children and adolescents

Onpattro is not recommended in children and adolescents under 18 years of age.

Other medicines and Onpattro

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. It is important to tell your doctor or nurse if you are taking any of the following medicines as your doctor may need to change the dose:

- Bupropion, a medicine used to treat depression or to help you to stop smoking
- Efavirenz, a medicine used to treat HIV infection and AIDS

Pregnancy, breast-feeding and contraception

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before starting this medicine.

Women of child-bearing age

Onpattro will reduce the level of vitamin A in your blood, which is important for normal development of your unborn child. If you are a woman of child-bearing age, you should practise effective contraception during treatment with Onpattro. Talk to your doctor or nurse about suitable methods of contraception. Pregnancy should be excluded before starting treatment with Onpattro.

Pregnancy

You should not use Onpattro if you are pregnant, unless advised by your doctor. If you are of child-bearing age and intend to use Onpattro, you should practise effective contraception.

Breast-feeding

Ingredients of Onpattro may pass into breast milk. Talk to your doctor about stopping breast-feeding or treatment with Onpattro.

Driving and using machines

Onpattro is believed to have no or negligible influence on the ability to drive or use machines. Your doctor will tell you whether your condition allows you to drive vehicles and use machines safely.

Onpattro contains sodium

This medicine contains 3.99 milligrams (mg) of sodium (main component of cooking/table salt) per millilitre (mL). This is 0.2% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Onpattro is given

How much Onpattro is given

- Your doctor will work out how much Onpattro to give you – this will depend on your body weight.
- The usual dose of Onpattro is 300 micrograms per kilogram (kg) of body weight given once every 3 weeks.

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’) usually over about 80 minutes.

If you do not have problems with your infusions in the clinic, your doctor may talk with you about a healthcare professional giving you your infusions at home.

Medicines given during treatment with Onpattro

About 60 minutes before each infusion of Onpattro, you will be given medicines that help to lower the risk of infusion-related reactions (see section 4). These include anti-histamines, a corticosteroid (a medicine that suppresses inflammation), and a pain reliever.

How long to use Onpattro

Your doctor will tell you how long you need to receive Onpattro. Do not stop treatment with Onpattro unless your doctor tells you to.

If you are given more Onpattro than you should receive

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 miss your dose of Onpattro

If you miss an appointment to have Onpattro, ask your doctor or nurse when to book your next treatment.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions

Infusion-related reactions are very common (may affect more than 1 in 10 people).

Tell your doctor or nurse straight away if you get any of the following signs of an infusion-related reaction during treatment. The infusion may need to be slowed down or stopped, and you may need to take other medicines to manage the reaction.

- Stomach pain
- Feeling sick (nausea)
- Body aches or pain, including pain in the back, neck, or joints
- Headache
- Feeling tired (fatigue)
- Chills
- Dizziness
- Cough, feeling short of breath, or other breathing problems
- Reddening of the face or body (flushing), warm skin, rash or itching
- Chest discomfort or chest pain
- Rapid heart rate
- Low or high blood pressure; some patients have fainted during the infusion due to low blood pressure
- Pain, redness, burning sensation, or swelling at or near the infusion site
- Swelling of the face
- Changes in the sound or tone of your voice (hoarseness)

Other side effects

Tell your doctor or nurse if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- Swelling of the arms or legs (peripheral oedema)

Common: may affect up to 1 in 10 people
- Pain in the joints (arthralgia)

- Muscle spasms
- Indigestion (dyspepsia)
- Shortness of breath (dyspnoea)
- Redness of the skin (erythema)
- Feeling dizzy or faint (vertigo)
- Stuffy or runny nose (rhinitis)
- Irritation or infection of the airways (sinusitis, bronchitis)

Uncommon: may occur in up to 1 in 100 infusions
- Leakage of the medicine into the surrounding tissue at the site of infusion, which may cause swelling or redness

Tell your doctor or nurse if you notice any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Onpattro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.

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.

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.

6. Contents of the pack and other information

What Onpattro contains

- The active substance is patisiran.
- Each mL contains patisiran sodium equivalent to 2 mg patisiran.
- Each vial contains patisiran sodium equivalent to 10 mg patisiran.
- The other ingredients are DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4- (dimethylamino) butanoate), PEG_{2000}-C-DMG (α- (3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene), DSPC (1,2-distearoyl-*sn*-glycero-3-phosphocholine), cholesterol, disodium hydrogen phosphate, heptahydrate, potassium dihydrogen phosphate, anhydrous, sodium chloride, and water for injections (see "Onpattro contains sodium" in section 2).

What Onpattro looks like and contents of the pack
- Onpattro is a white to off-white, opalescent, homogeneous concentrate for solution for infusion (sterile concentrate).

- Onpattro is supplied in cartons containing one vial each.

Marketing Authorisation Holder and Manufacturer

Alnylam Netherlands B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Required premedication

All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs). 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 (intravenous, IV), or equivalent. The patient should receive at least 3 consecutive 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.

Preparation of the solution for infusion

This medicinal product is for single-use only.

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.
- 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.
- Onpattro does not contain preservatives. The diluted solution should be administered immediately after preparation. If not used immediately, store the diluted solution in the infusion bag at room temperature (up to 30°C) or at 2°C to 8°C for up to 16 hours (including infusion time). Do not freeze.

Administration

Onpattro is for intravenous use.

- Onpattro must be diluted prior to intravenous infusion.
- A dedicated line with an infusion set containing a 1.2 micron PES in-line infusion filter must be used. The infusion sets 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.
- Onpattro must be administered through a secure and 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.
- 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.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for patisiran, the scientific conclusions of CHMP are as follows:

In view of available data on dysphonia from clinical trial(s), and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between patisiran and dysphonia is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing patisiran should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for patisiran the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing patisiran is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.