Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Patisiran-LNP 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: 6.3 – 7.5).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Patisiran-LNP is indicated for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

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 patisiran-LNP is 300 micrograms per kg 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 patisiran-LNP (see section 4.4).

Required premedication
All patients should receive premedication prior to patisiran-LNP 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 patisiran-LNP 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 premedication not available or not tolerated intravenously, equivalents may be administered orally.

If clinically indicated, the corticosteroid may be tapered in decrements no greater that 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 patisiran-LNP 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, patisiran-LNP should be administered as soon as possible.
- If patisiran-LNP is administered within 3 days of the missed dose, dosing should be continued according to the patient's original schedule.
- If patisiran-LNP 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 ULN and AST > 1 x ULN, or bilirubin > 1.0 to 1.5 x ULN and any AST). Patisiran-LNP 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).

Liver transplant
Patisiran-LNP 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). Patisiran-LNP 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 patisiran-LNP in children or adolescents < 18 years of age have not been established. No data are available.

Method of administration

Patisiran-LNP is for intravenous use.

- Patisiran-LNP must be diluted prior to intravenous infusion (see instructions in 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 patisiran-LNP 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).
- Patisiran-LNP 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 0.9% solution to ensure that all medicinal product has been administered.

Infusion of patisiran-LNP 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 patisiran-LNP. 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.

To reduce the risk of IRRs, patients should receive premedications on the day of patisiran-LNP 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 patisiran-LNP 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, patisiran-LNP 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 with patisiran-LNP.

Patients receiving patisiran-LNP 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 patisiran-LNP (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 patisiran-LNP and women of childbearing potential should practise effective contraception. If a woman intends to become pregnant, patisiran-LNP 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, patisiran-LNP 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 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.

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 medicinal products and other forms of interaction

No formal clinical drug interaction studies have been performed. Patisiran-LNP is 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.

Vitamin A testing

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with patisiran-LNP 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 patisiran-LNP, 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 patisiran-LNP 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 initation 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 patisiran-LNP 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, patisiran-LNP 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 patisiran-LNP.

Breast-feeding

It is unknown whether patisiran-LNP is excreted in human milk. 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 patisiran-LNP, 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 patisiran-LNP 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, patisiran-LNP 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 patisiran-LNP-treated patients were peripheral oedema (29.7%) and infusion-related reactions (18.9%). The only adverse reaction resulting in the discontinuation of patisiran-LNP 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 patisiran-LNP 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, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, 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 patisiran-LNP-treated patients experienced IRRs, compared to 9.1% of placebo-treated patients. In patisiran-LNP-treated patients, all IRRs were either mild (95.2%) or moderate (4.8%) in severity. Among patisiran-LNP-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 patisiran-LNP 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 patisiran-LNP-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 patisiran-LNP-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 patisiran-LNP were evaluated by measuring antibodies specific to PEG_{2000}-C-DMG, a lipid component exposed on the surface of patisiran-LNP. 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 patisiran-LNP. 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 patisiran-LNP.

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: not yet assigned; ATC code: not yet assigned.

Mechanism of action
Patisiran-LNP contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA) that specifically targets a genetically conserved sequence in the 3' untranslated region of all mutant and wild-type TTR mRNA. Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through a natural process called RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA 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 patisiran-LNP. 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 patisiran-LNP 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 patisiran-LNP 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 patisiran-LNP 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 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 patisiran-LNP group had a non-V30M mutation (62% vs. 48%). Ninety-three percent (93%) of patisiran-LNP-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 patisiran-LNP 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 patisiran-LNP 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 patisiran-LNP-treated patients versus 3.9% of placebo-treated patients experienced improvement in mNIS+7 ($p < 0.001$).

Patients treated with patisiran-LNP demonstrated statistically significant benefits in the primary endpoint and 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 patisiran-LNP to placebo was observed across all domains of Norfolk QoL-DN, and 51.4% of patisiran-LNP-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)		(Patisiran-LNP – Placebo) Treatment Difference, LS Mean (95% CI)	p-value
	Patisiran-LNP N=148	Placebo N=77	Patisiran-LNP	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

Patients receiving patisiran-LNP 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 patisiran-LNP 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 patisiran-LNP-treated and placebo-treated patients, respectively. At 18 months, the adjusted geometric mean ratio to baseline was 0.89 with patisiran-LNP and 1.97 with placebo (ratio, 0.45; p < 0.001), representing a 55% difference in favour of patisiran-LNP.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with patisiran-LNP 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 patisiran-LNP 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 concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_{τ}) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_{τ} was 3.2-fold at steady-state compared to the first dose.

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 patisiran-LNP 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 ($t_{1/2\beta}$) 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 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 patisiran-LNP 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 patisiran-LNP 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. Patisiran-LNP 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. Patisiran-LNP 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 patisiran-LNP led to increases in serum liver markers (ALT, AST, ALP, and/or total bilirubin) and histopathology findings in the liver (hepatocellular/single cell necrosis, inflammation, pigment deposition, and/or monocytic infiltration) at doses > 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

Patisiran-LNP did not exhibit a genotoxic potential in vitro and in vivo 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, patisiran-LNP generated spontaneous abortions, reduced embryo-foetal survival, and reduced foetal body weights at maternally toxic doses ≥ 1 mg/kg (HED 3.2 times the 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 patisiran-LNP 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
2 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, patisiran-LNP 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

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 and other handling

This medicinal product is for single-use only.

Patisiran-LNP must be diluted with sodium chloride 0.9% solution prior to intravenous infusion. The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique as follows:

1. Remove patisiran-LNP from the refrigerator. Do not shake or vortex.
2. Discard vial if it has been frozen.
3. Inspect visually for particulate matter and discolouration. Do not use if discolouration or foreign particles are present. Patisiran-LNP 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.
4. Calculate the required volume of patisiran-LNP based on the recommended weight-based dosage (see section 4.2).

If using a 0.45 micron syringe filter

5. Withdraw the entire contents of one or more vials into a single sterile syringe and filter patisiran-LNP through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.

If using a 0.2 micron syringe filter

5. Withdraw the entire contents of one vial into a sterile syringe and filter through a sterile 0.2 micron polyethersulfone (PES) syringe filter into a sterile container. Repeat this step for additional vials as needed, **using a new filter for each vial**.

6. Withdraw the required volume of filtered patisiran-LNP from the sterile container using a sterile syringe.
7. Dilute the required volume of filtered patisiran-LNP into an infusion bag containing sodium chloride 0.9% solution for a total volume of 200 mL. Use infusion bags that are free of DEHP.
8. Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs.
9. Discard any unused portion of patisiran-LNP. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Alnylam UK Limited
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Braywick Road
Maidenhead
SL6 1DA
United Kingdom

8. EAMS NUMBER(S)

43942/0001

9. DATE OF SCIENTIFIC OPINION 2nd August 2018
Additional information: To request supply of patisiran-LNP through EAMS, a Physician Declaration and Patient Access Form must be read, completed and signed by the treating physician. A copy of the relevant forms can be requested by submitting a request to EAP@alnylam.com. Following confirmation of eligibility by Alnylam, physicians will be provided with the program-related materials.
Contact information: All reporting forms should be reported to Medpace Clinical Safety using the reporting details below: **Medpace Clinical Safety Europe** 26-28 Hammersmith Grove London, W6 7HA, United Kingdom SAE Hotline: +49 89 89 55 718 44 (p) Safety Fax: +49 89 89 55 718 104 (f) Medpace Clinical Safety: Medpace-safetynotification@medpace.com General EAMS related enquiries: EAP@alnylam.com