Summary of risk management plan for Onpattro (patisiran)

This is a summary of the risk management plan (RMP) for Onpattro. The RMP details important risks of Onpattro, how these risks can be minimized, and how more information will be obtained about Onpattro's risks and uncertainties (missing information).

Onpattro's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Onpattro should be used.

This summary of the RMP for Onpattro should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Onpattro's RMP.

I. The medicine and what it is used for

Onpattro is authorized for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. It contains patisiran as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Onpattro's benefits can be found in Onpattro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/onpattro.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Onpattro, together with measures to minimize such risks and the proposed studies for learning more about Onpattro's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Onpattro, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Onpattro is not yet available, it is listed under 'missing information'.

II.A List of important risks and missing information

Important risks of Onpattro are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Onpattro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risk	• Infusion-related reactions
Important potential risks	• Consequences of vitamin A deficiency • Severe hypersensitivity • Hepatic disorders
Missing information	• Longer-term safety (>3 years) • Use in patients with moderate or severe hepatic impairment • Use in patients with severe renal impairment or end-stage renal disease • Use in patients with prior liver transplantation • Use in pregnancy and lactation

II.B Summary of important risks

Important Identified Risk: Infusion-Related Reactions (IRRs)	
Evidence for linking the risk to the medicine	Infusion-related reactions (IRRs) were reported in clinical studies of Onpattro and included such signs and symptoms as back pain, flushing, nausea, and headache. This group of symptoms was reported more frequently in patients receiving Onpattro than in patients receiving placebo in a double-blind, randomized, placebo-controlled pivotal Phase 3 clinical study. IRRs were noted in other clinical studies of Onpattro. Patients received premedications (corticosteroid, antihistamines, and paracetamol) to reduce the risk of IRRs. IRRs were mostly mild in severity and decreased in frequency over time. Few infusions had to be interrupted, and among those that were, most continued until the full dose was administered.
Risk factors and risk groups	In general, it is difficult to predict which patients in a population may be more susceptible to IRRs. However, it is known that IRRs may be prevented or the symptoms made less severe by the administration of premedication.[a,b] Controlling how fast the drug is infused is also important to help decrease the number and severity of IRRs.

Important Identified Risk: Infusion-Related Reactions (IRRs)	
Risk minimization measures	Routine risk minimization measures: • Description of the proportion of patients with, frequency, nature and severity of IRRs is provided in Section 4.4 and Section 4.8 of the SmPC • Description of IRRs is provided in Section 2 and Section 4 of the Package Leaflet • Onpattro therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis (Section 4.2 of the SmPC) • Premedication is required, and recommended medications, dosages, and timing are described in Section 4.2 of the SmPC and Section 3 of the Package Leaflet • Instructions on the recommended rate of infusion are provided in Section 4.2 of the SmPC • Recommendations for medical management of an IRR, if it occurs, including interruption or slowing of the Onpattro infusion rate and/or instituting medical management as clinically indicated (Section 4.4 of the SmPC) • Information that 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 (Section 4.4 of the SmPC) • Instructions that the decision for whether a patient can receive infusions at home should be made by the treating physician, and may be considered for patients who have tolerated well at least 3 infusions well in the clinic (Section 4.2 of the SmPC). Home infusion should be performed by a healthcare professional • Legal status: restricted medical prescription Additional risk minimization measures: • Educational Materials for HCPs and patients to optimize the safe administration of patisiran in the home

[a] Doessegger and Banholzer, Clin Tranl Immunology, 2015 Jul;4(7):e39.
[b] Szebeni, Mol Immunol, 2014 Oct;61(2):163-73.

Important Potential Risk: Consequences of Vitamin A Deficiency	
Evidence for linking the risk to the medicine	The primary mechanism of action of Onpattro is to reduce the level of transthyretin (TTR). One function of TTR is to carry retinol binding protein (RBP), which distributes vitamin A in serum. There is, therefore, a theoretical risk of vitamin A deficiency. However, vitamin A can be distributed into tissues without RBP.[a,b,c] RBP and serum vitamin A were reduced in studies of Onpattro in monkeys; however, no evidence of vitamin A deficiency was observed. Patients in the clinical studies were advised to take vitamin A supplementation at the usual recommended daily

Important Potential Risk: Consequences of Vitamin A Deficiency	
	dose. No symptoms of vitamin A deficiency such as night blindness or other eye conditions were seen in patients receiving Onpattro.
Risk factors and risk groups	Prolonged dietary deficiency and other conditions such as gastrointestinal malabsorption due to a variety of causes can lead to vitamin A deficiency in the hATTR amyloidosis population.
Risk minimization measures	<u>Routine risk minimization measures:</u> • The secondary pharmacologic effect of Onpattro on serum vitamin A levels is described in Section 4.4, Section 4.5, Section 4.6, and Section 5.1 of the SmPC • Recommendation that serum vitamin A levels below lower limit of normal should be corrected and any ocular symptoms due to vitamin A deficiency be evaluated prior to initiation of treatment (Section 4.4 of the SmPC and Section 2 of the Package Leaflet) • Recommendation for vitamin A supplementation of approximately 2500 IU per day (Section 4.2 and Section 4.4 of the SmPC and guidance for patients in Section 2 of the Package Leaflet • Recommendation not to use serum vitamin A levels to guide vitamin A supplementation (Section 4.4 and 4.5 of the SmPC) • If a patient develops ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness), referral to an ophthalmologist is recommended (Section 4.4 of the SmPC) and patients are advised to talk to their doctor if they notice a change in their vision (Section 2 of the Package Leaflet) • A statement that vitamin A levels that are too high or too low may be associated with an increased risk of foetal malformation has been added in Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet, and recommendation that pregnancy should be excluded before treatment initiation. Women of childbearing potential should practise effective contraception during patisiran treatment (Section 4.4 and 4.6 of the SmPC and Section 2 of the Package Leaflet). Recommendation to monitor vitamin A levels, to modify vitamin A supplementation for pregnancy (planned and unplanned), and monitoring of the foetus have been added to Section 4.4 and 4.6 of the SmPC. • Legal status: restricted medical prescription

[a] Biesalski et al, Am J Clin Nutr, 1999 May;60(5):931-6.

[b] Episkopou et al, Proc Natl Acad Sci U S A, 1993 Mar 15;90(6):2375-9.

[c] van Bennekum et al, J Biol Chem, 2001 Jan 12;276(2):1107-13.

Important Potential Risk: Severe Hypersensitivity	
Evidence for linking the risk to the medicine	Severe hypersensitivity is a theoretical risk for any drug, but has not been observed in patients taking Onpattro.

Important Potential Risk: Severe Hypersensitivity	
Risk factors and risk groups	Patients with a history of severe hypersensitivity to patisiran or any of the excipients are clearly at higher risk. Patients with a personal history of atopy may be at higher risk in general; however, there are no specific data to suggest that these patients would be at higher risk of a reaction to Onpattro.
Risk minimization measures	Routine risk minimization measures: • Statement that Onpattro is contraindicated in patients with severe hypersensitivity (e.g., anaphylaxis) to the active substance or any of the excipients in Section 4.3 of the SmPC and Section 2 of the Package Leaflet • Legal status: restricted medical prescription

Important Potential Risk: Hepatic disorders	
Evidence for linking the risk to the medicine	Hepatoxicity was observed in the nonclinical studies in rodents and monkey. In the placebo-controlled Phase 3 study, there was no increase in hepatic adverse events in patients treated with patisiran compared to patients treated with placebo. A small increase of ALT and AST from baseline was observed in the patisiran group compared with placebo that remained stable for the 18-month treatment period. The changes in ALT and AST were not associated with changes in ALP or total bilirubin. Similar results were observed in the open-label extension studies. Across the 3 studies, ALT and AST levels remained stable over time for periods up to 84.9 months.
Risk factors and risk groups	Patients with hepatic impairment or liver transplants may be at higher risk for hepatic disorders.
Risk minimization measures	Routine risk minimization measures: • Legal status: restricted medical prescription
Additional pharmacovigilance activities	• Evaluation of data from the open-label extension Study ALN-TTR02-006 • Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Longer-term Safety (>3 years)	
Risk minimization measures	Routine risk minimization measures: • A summary of the safety profile of Onpattro and duration of exposure in the clinical development program is provided in Section 4.8 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the open-label extension Study ALN-TTR02-006 • Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of data in patients with moderate and severe hepatic impairment is included in Section 4.2 of the SmPC. A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild hepatic impairment in Section 5.2 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Severe Renal Impairment or End-stage Renal Disease	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of data in patients with severe renal impairment or end-stage renal disease is included in Section 4.2 of the SmPC. A statement that patisiran should not be used in these patients unless the anticipated clinical benefit outweighs the potential risk is included in Section 4.2 of the SmPC. This section includes cross-reference to the rationale for not recommending dose adjustment in patients with mild or moderate renal impairment in Section 5.2 of the SmPC
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Patients with Prior Liver Transplantation	
Risk minimization measures	Routine risk minimization measures: • Section 4.8 of the SmPC states that 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. • Section 5.1 of the SmPC states that 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. • Section 5.2 of the SmPC states that in a clinical study in hATTR amyloidosis patients who had undergone prior liver transplant, steady

Missing Information: Use in Patients with Prior Liver Transplantation	
	state pharmacokinetic parameters and TTR reduction were comparable to those observed in patients without a liver transplant.
Additional pharmacovigilance activities	• Evaluation of data from the non-interventional observational cohort Study 009

Missing Information: Use in Pregnancy and Lactation	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of clinical data in pregnant and lactating women is included in Section 4.6 of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in Section 5.3 of the SmPC • Recommendation for use of effective contraception in women of childbearing potential is provided in Section 4.4 and Section 4.6 of the SmPC and Section 2 of the Package Leaflet
Additional pharmacovigilance activities	• Evaluation of data from the Global Pregnancy Surveillance Program Study 010 to collect and evaluate data on pregnancy exposure and infant outcomes

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Onpattro.

II.C.2 Other studies in post-authorization development plan

Study ALN-TTR02-006, Ongoing, Open-label, Long-term, Safety Extension Study

Purpose of the study: This is an ongoing, open-label, long-term, interventional extension study to assess the safety and efficacy of longer-term Onpattro dosing in adult patients with hATTR amyloidosis with polyneuropathy who completed and tolerated study treatment in the double-blind, randomized, placebo controlled pivotal Phase 3 study (Study ALN-TTR02-004) and a prior open-label Phase 2 extension study (Study ALN-TTR02-003).

Study ALN-TTR02-009, Prospective Observational Cohort Study

This non-interventional observational cohort study will provide real-world experience from patisiran use, as well as provide comparative safety data from other treatments, or no treatment, that can be used to further assess the findings and any association with patisiran. The study cohort will include all patients with hATTR amyloidosis under care at the participating clinics, as no exclusion criteria are intended with this observational cohort. Patients treated at home, as well as patients with hepatic or renal impairment, and patients with prior liver transplantation will be observed as part of the cohort. The planned size of the total hATTR amyloidosis study cohort is 300 patients and will include 150 patients exposed to patisiran over a period of up to

10 years from the time the first patient is treated with patisiran post-authorization. The study is targeting to evaluate at least 900 patient-years of patient experience on patisiran.

Study ALN-TTR02-010, Global Pregnancy Surveillance Program

This global pregnancy surveillance program will collect and evaluate information on exposure during pregnancy and infant outcomes in patients with hATTR amyloidosis who are exposed to patisiran. As of the data lock point of this RMP, no patients have enrolled in Study ALN-TTR02-010.