Date: 13 November 2019
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

ONPATTRO

International non-proprietary name: Patisiran
Pharmaceutical form: Concentrate for solution for infusion
Dosage strength: 300 micrograms per kg body weight once every 3 weeks
Route(s) of administration: Intravenous use
Marketing Authorisation Holder: Alnylam Switzerland GmbH
Marketing Authorisation No: 67304
Decision and Decision date: approved on 23 September 2019

Note:

Assessment Report as adopted by Swissmedic with all information of commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices TPA (SR 812.21). The agency ensures that only high quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products TPO (SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibodies
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 8 November 2018.

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA. The reduced assessment procedure was accepted on 22 January 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

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.
Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised for patients treated with Onpattro.
Required premedication
All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs).

2.2.4 Approved Dosage

(see appendix).

2.3 Regulatory History (Milestones)

Application	03 January 2019
Formal control completed	22 January 2019
Predecision	28 May 2019
Answers to Predecision	19 July 2019
Final Decision	23 September 2019
Decision	approval

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Swissmedic has not assessed the primary data of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR refers to the publicly available EMA Assessment Report for ONPATTRO, published 30 October 2018, EMA/554262/2018.

3 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR relating to quality aspects refers to the publicly available EMA Assessment Report for ONPATTRO, published 30 October 2018, EMA/554262/2018.

4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR relating to preclinical aspects refers to the publicly available EMA Assessment Report for ONPATTRO, published 30 October 2018, EMA/554262/2018.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency (EMA). The current SwissPAR relating to clinical aspects refers to the publicly available EMA Assessment Report for ONPATTRO, published 30 October 2018, EMA/554262/2018.

5.1 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to ONPATTRO was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference documents, which are valid and relevant for the effective and safe use of medicinal products in Switzerland, are the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The MAH is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are encouraged to report the suspicion of a new or serious side effect. Information on the reporting of side effects, see section "Undesirable effects".

ONPATTRO®

Composition

Active substance:
Patisiran (as Patisiran-Sodium)

Excipients:
DLin-MC3-DMA ((6Z,9Z,28Z,31Z)-Heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)-butanoate), 1,2-Dimyristoyl-*sn*-glycero-3-carboxaminopropyl polyethyleneglycol-2000-methylether (PEG_{2000}-C-DMG), 1,2-Distearoyl-*sn*-glycero-3-phosphatidylcholine (DSPC), cholesterol, disodium hydrogen phosphate heptahydrate, potassium dihydrogen phosphate, sodium chloride, water for injections; contains 3.99 mg of sodium per mL.

Pharmaceutical form and quantity of active substance per unit

Concentrate for solution for infusion (sterile concentrate).

Appearance
White to off-white, opalescent, homogeneous solution.

Quantity of active substance per unit
Each mL contains 2 mg patisiran (as patisiran-sodium). Each vial of 5 mL contains 10 mg patisiran (as patisiran-sodium), formulated as lipid nanoparticles.

Indications/Applications

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

Dosage/Administration

Therapy should be initiated in a centre for neuromuscular diseases under the supervision of a physician knowledgeable in the management of amyloidosis. Also continued treatment should be provided by a physician experienced in the treatment of polyneuropathy.

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

Dosing is based on actual body weight. For patients weighing ≥ 100 kg, the maximum recommended dose is 30 mg.

Vitamin A supplementation at approximately 2500 IU vitamin A per day is advised for patients treated with Onpattro (see «Warnings and Precautions»).

Required premedication

All patients should receive premedication prior to Onpattro administration to reduce the risk of infusion-related reactions (IRRs) (see «Warnings and Precautions»). 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 «Warnings and Precautions» and «Undesirable Effects»).

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). 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 «Pharmacokinetics»).

Liver transplant

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

Renal impairment

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

Elderly patients

No dose adjustment is required in patients ≥ 65 years of age (see «Pharmacokinetics»).

Paediatric population

The safety and efficacy of Onpattro in children or adolescents < 18 years of age has not been shown. There is no data available.

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.

Method of administration

Onpattro, concentrate for solution for infusion, is for intravenous use.

- Onpattro must be diluted prior to intravenous infusion (see «Instructions for use»).
- 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 «Warnings and Precautions»).
- 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 «Warnings and Precautions»).
- 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.

Contraindications

Hypersensitivity to the active substance or any of the excipients according to «Composition».

Warnings and Precautions

Infusion-Related Reactions, IRRs

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 «Undesirable Effects»). Across clinical studies, the most common symptoms (reported in ≥ 2% of patients) of IRRs were flushing, back pain, nausea, abdominal pain, dyspnoea, and headache.

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 «Indications/Applications»). If an IRR occurs, slowing or interrupting the infusion and institution of medical management (e.g., corticosteroids or other symptomatic treatment) should be considered, as clinically indicated. If the infusion is interrupted, resumption of the infusion at a slower infusion rate may be considered after symptoms have resolved. The Onpattro infusion should be discontinued in the case of a serious or life-threatening IRR.

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

Vitamin A deficiency

By reducing serum transthyretin (TTR) protein, Onpattro treatment leads to a decrease in serum vitamin A (retinol) levels (see «Properties/Effects»). Prior to initiation of treatment with Onpattro 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.

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

Serum vitamin A levels should not be used to guide vitamin A supplementation during treatment with Onpattro (see «Interactions»).

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 «Pregnancy/Lactation»). Vitamin A supplementation should be discontinued during the first trimester, unless the pregnant woman has clinical signs of vitamin A deficiency. If such signs are present, vitamin A supplementation should not exceed 2500 IU per day. Thereafter, vitamin A supplementation of 2500 IU per day should be resumed in the second and third trimesters if serum vitamin A levels have not returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

Other ingredients
This medicinal product contains 19.95 mg sodium per vial, equivalent to 1% of the WHO recommended maximum daily sodium intake of 2 g.

Interactions
No formal clinical drug interaction studies have been performed. Onpattro 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.

Other interactions
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 «Warnings and Precautions» and «Properties/Effects»).

Pregnancy/Lactation

Women of child-bearing age

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 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 sufficient data on the use of Onpattro in pregnant women.

There are no adequate animal studies on the effects on pregnancy, embryonic development, fetal development and / or postnatal development (see «Preclinical Data»).

Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Onpattro should not be used during pregnancy, unless it is clearly necessary.

As a precautionary measure, vitamin A and thyroid stimulating hormone (TSH) levels should be obtained early in pregnancy (see «Preclinical Data»). Close monitoring of the foetus should be carried out in the event of an unplanned pregnancy, especially during the first trimester (see «Warnings and Precautions»).

Lactation

It is unknown whether Onpattro 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 «Preclinical Data»).

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 «Preclinical Data»).

Effects on ability to drive and use machines
No studies have been done.
Based on studies on pharmacokinetics and pharmacodynamics Onpattro is considered to have no or negligible impact on the ability to drive or use machines.

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%).
The only adverse reaction resulting in the discontinuation of Onpattro was an infusion-related reaction (0.7%).

The following list of adverse reactions is based on observations from clinical trials in adults.
The adverse reactions are arranged by organ system and according to frequency (number of patients expected to experience the reaction) using the following categories: «Very common» (≥1/10), «common» (<1/10, ≥1/100), «occasionally» (≥1/1000 bis <1/100), «rare» (≥1/10‘000 bis <1/1000), «very rare» (<1/10‘000).

Infections and parasitic diseases
Common: Bronchitis, Sinusitis, Rhinitis

Immune system disorders
Very common: Infusion-related reaction (18.9 %)

Ear and labyrinth disorders
Common: Vertigo

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea

Gastrointestinal disorders
Common: Dyspepsia

Skin and subcutaneous tissue disorders
Common: Erythema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, Muscle spasms

General disorders and administration site conditions
Very common: Peripheral oedema (29.7 %)
Uncommon: Extravasation

Description of selected side effects
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 Onpattro-treated patients experienced IRRs, compared to 9.1% of placebo-treated patients. In Onpattro-treated patients, all IRRs

were either mild (95.2%) or moderate (4.8%) in severity. Among Onpattro-treated patients who experienced an IRR, 78.6% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. Few IRRs led to infusion interruption. IRRs resulted in permanent discontinuation of Onpattro in < 1% of patients in clinical studies. For clinical management of IRRs, see «Warnings and precautions».

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

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

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

The reporting of suspected adverse reactions after approval is of great importance. It allows continuous monitoring of the benefit-risk balance of the drug. Healthcare professionals are encouraged to report any suspicion of a new or serious side effect via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

Overdose

Cases of overdose were not reported.

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.

Properties/effects

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 mutant and wild-type transthyretin (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 «Warnings and precautions» and «Interactions»).

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 (not approved in Switzerland). Forty-nine percent (49%) and 50% of patients had a New York Heart Association (NYHA) Class of I or II, respectively. Approximately half of patients (56%) met pre-defined criteria for cardiac involvement (defined as baseline LV wall thickness ≥ 13 mm with no history of hypertension or aortic valve disease). Patient demographics and baseline characteristics were balanced between treatment groups, except that a higher proportion of patients in the Onpattro group had a non-V30M 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 1). 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 1).

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 1: 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.

Paediatrics
Swissmedic has waived the obligation to submit the results of studies with Onpattro in all subsets of the paediatric population in hATTR amyloidosis (see «Dosage/Administration» for paediatric population).

Pharmacokinetics
Absorption
Greater than 95% of patisiran in the circulation is associated with lipid nanoparticles. At the dose regimen of 300 micrograms per kg every 3 weeks, steady state was reached by 24 weeks of treatment. The estimated patisiran mean ± SD steady-state peak concentration (C_{max}), trough concentration (C_{trough}), and area under the curve (AUC_{τ}) were 7.15 ± 2.14 µg/mL, 0.021 ± 0.044 µg/mL, and 184 ± 159 µg·h/mL, respectively. The accumulation of AUC_{τ} was 3.2-fold at steady-state compared to the first dose.

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

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

Distribution

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

Metabolism

Patisiran is 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 relationships
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 «Interactions»). Patisiran is not a substrate of cytochrome P450 enzymes.

Kinetics of special patient groups
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.

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

Renal impairment
Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild or moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m^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.

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.

Preclinical data
Liver and spleen were the primary target organs of toxicity in both rats and monkeys. Intravenous administration of Onpattro led to increases in serum liver markers (ALT, AST, ALP, and/or total bilirubin) and histopathology findings in the liver (hepatocellular/single cell necrosis, inflammation, pigment deposition, and/or monocytic infiltration) at doses > 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.

Mutagenicity and 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 (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 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.

Other Information

Incompatibilities

The medicinal product must only be mixed with the medicinal products listed under «Instructions for use».

Shelf life

This medicinal product should only be used up to the date indicated with “EXP” on the packaging.

In-use stability

The diluted infusion preparation does not contain a preservative. Chemical and physical in-use stability has been demonstrated for up to 16 hours at up to 30 °C. For microbiological reasons, the ready-to-use preparation should be used immediately after dilution.

Special storage instructions

Store in a refrigerator (2°C to 8°C).
Do not freeze.

If refrigeration is not available, Onpattro can be stored at room temperature (15-25°C) for up to 14 days.

Keep out of the reach of children.

Instructions for Use
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 «Dosage/Administration»).
- Withdraw the entire contents of one or more vials into a single sterile syringe.
- Filter Onpattro through a sterile 0.45 micron polyethersulfone (PES) syringe filter into a sterile container.
- Withdraw the required volume of filtered Onpattro from the sterile container using a sterile syringe.
- Dilute the required volume of filtered Onpattro into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for a total volume of 200 mL. Use infusion bags that are free of di(2-ethylhexyl)phthalate (DEHP).
- Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other medicinal products.
- Discard any unused portion of Onpattro. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Marketing authorisation number

67304 (Swissmedic)

Packs

Onpattro 5 mL concentrate in a Type I glass vial with a chlorobutyl stopper and an aluminium flip-off cap. (B)

Pack size of 1 vial.

Marketing Authorisation Holder

Alnylam Switzerland GmbH, Zug

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