RISK MANAGEMENT PLAN SUMMARY
FOR
AMVUTTRA® (VUTRISIRAN)

Amvuttra 25 mg, Injektionslösung in einer Fertigspritze
ZL-Nr.: 69074

Alnylam Switzerland GmbH

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Amvuttra is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Amvuttra in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Alnylam Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Amvuttra.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ATTR amyloidosis	Transthyretin-mediated amyloidosis
EU	European Union
GalNAc	*N*-acetylgalactosamine
hATTR amyloidosis	Hereditary transthyretin-mediated amyloidosis
mNIS+7	Modified neuropathy impairment score +7
mRNA	Messenger ribonucleic acid
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy
PD	Pharmacodynamic
PK	Pharmacokinetic
PV	Pharmacovigilance
qM	Once monthly
qw	Once weekly
q3w	Once every 3 weeks
RBP	Retinol binding protein
RMP	Risk Management Plan
RNAi	RNA interference
SC	Subcutaneous
siRNA	Small interfering ribonucleic acid
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TTR	Transthyretin
US	United States
wt	Wild-type
wtATTR amyloidosis	Wild-type transthyretin-mediated amyloidosis

SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR AMVUTTRA

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

Amvuttra's summary of product characteristics (SmPC) and its patient information leaflet (PIL) give essential information to healthcare professionals and patients on how Amvuttra should be used.

This summary of the RMP for Amvuttra 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 Amvuttra's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Amvuttra is authorised for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with polyneuropathy. It contains vutrisiran as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Amvuttra's benefits can be found in Amvuttra's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PIL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including in the Periodic Safety Update Report 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 Amvuttra is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Amvuttra are risks that need special risk management activities to further investigate or minimise 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 Amvuttra. 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 (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• None
Important potential risk	• Clinical consequences of vitamin A deficiency, including delayed symptoms • Hypersensitivity reactions
Missing information	• Longer-term safety (>2 years) • Use in patients with moderate or severe hepatic impairment • Use in pregnant women and effects on pregnancy outcomes

II.B Summary of Important Risks

Important Potential Risk: Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms	
Evidence for linking the risk to the medicine	The primary mechanism of action of Amvuttra is to reduce the level of transthyretin (TTR). Serum TTR is a carrier of retinol binding protein (RBP), which helps transport vitamin A in the blood. Therefore, there is a theoretical risk of vitamin A deficiency when TTR levels are reduced. However, there is evidence that vitamin A can be transported to tissues without RBP.[Biesalski 1999; Episkopou 1993] In studies of Amvuttra in mice and monkeys, RBP and serum vitamin A were reduced; however, no evidence of vitamin A deficiency was observed. Patients in the clinical study were advised to take vitamin A supplementation at the usual recommended daily dose.
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.

Important Potential Risk: Clinical Consequences of Vitamin A Deficiency, Including Delayed Symptoms	
Risk minimisation measures	Routine risk minimisation measures: • The secondary pharmacologic effect on serum vitamin A levels is described in SmPC sections 4.4, 4.5, 5.1, and 5.3, and PIL Section 2. • Legal status: Prescription-only Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing):** • Evaluation of data from the HELIOS-A RTE **Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study** • Evaluation of data from the ConTTRibute Study

Abbreviations: hATTR=Hereditary transthyretin-mediated amyloidosis; PIL=patient information leaflet; RBP= Retinol binding protein; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

[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.

Important Potential Risk: Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	Hypersensitivity is a theoretical risk for any drug. In the vutrisiran group of the HELIOS-A study, 2 patients had a single event of drug hypersensitivity. Neither event was serious or considered related to study drug. In addition, 3 (2.5%) patients had a total of 3 treatment-related events erythema, pruritus, and rash) mapped to the Hypersensitivity SMQ (scope: narrow and broad). None were severe or serious. One patient experienced 6 severe events (dizziness, dry mouth, hyperhidrosis, hyperthermia, scleral discolouration, and dyspepsia) within 2 days of their first dose of vutrisiran as well as additional mild or moderate events within 2 days of subsequent doses. While the pattern of variable tolerance did not suggest anaphylaxis, a drug hypersensitivity reaction could not be ruled out.
Risk factors and risk groups	Patients with hypersensitivity to vutrisiran or any of the excipients are 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 vutrisiran.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 and PIL Section 2 • Legal status: Prescription-only Additional risk minimisation measures: • None

Important Potential Risk: Hypersensitivity Reactions	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing):** • Evaluation of data from the HELIOS-A RTE **Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study** • Evaluation of data from the ConTTRibute Study

Abbreviations: PIL=patient information leaflet; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics; SMQ=standardized MedDRA query.

Missing Information: Longer-term safety (>2 years)	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: **Study ALN-TTRSC02-002, HELIOS-A: Randomised Treatment Extension (Ongoing):** • Evaluation of data from the HELIOS-A RTE **Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study** • Evaluation of data from the ConTTRibute Study

Abbreviation: RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

Missing Information: Use in patients with moderate or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	**Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study:** • Evaluation of data from the ConTTRibute Study

Abbreviation: SmPC=Summary of Product Characteristics.

Missing Information: Use in pregnant women and effects on pregnancy outcomes	
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.4, 4.6, and 5.3, and PIL Section 2 Additional risk minimisation measures: • None

Missing Information: Use in pregnant women and effects on pregnancy outcomes	
Additional pharmacovigilance activities	**Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study:** • Evaluation of data from the ConTTRibute study

Abbreviations: PIL= Patient information leaflet; SmPC=Summary of Product Characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Amvuttra.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study: HELIOS-A Randomised Treatment Extension (Ongoing)

Purpose of the study: The HELIOS-A-RTE study is a Phase 3 global, open-label study to evaluate the safety and efficacy of ALN-TTRSC02 in patients with hATTR Amyloidosis. The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.

Study ALN-TTR02-013, ConTTRibute Study: Global, Prospective, Observational, Multicenter Long-Term Study (Ongoing; protocol to be amended to include vutrisiran)

Purpose of the study: This is a prospective, observational study that will provide a robust assessment of the long-term safety of Amvuttra in real-world clinical practice along with a comparator group being enrolled in ConTTRibute who follow local standard of care. ConTTRibute aims to document the natural history, clinical characteristics, and management of ATTR amyloidosis as part of routine clinical care. The study cohort will include patients with hATTR amyloidosis under care at the participating study site, as no exclusion criteria are intended with this observational cohort. Patients with hepatic impairment will be observed as part of the cohort. The study will also include data collection on the clinical consequences of vitamin A deficiency, including delayed symptoms, and pregnancy exposure and pregnancy and infant outcomes.