Product Monograph

Including Patient Medical Information

Product Monograph

Including Patient Medication Information

Pr**AMVUTTRA**®

vutrisiran injection

solution

For subcutaneous injection use

25 mg/0.5 mL of vutrisiran (as vutrisiran sodium)

other nervous system drugs

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

Imported / Distributed by:
Innomar-Strategies
Oakville, ON
L6L 0C4

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Recent Major Label Changes

There are no recent major changes to this Product Monograph.

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

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

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2. Contraindications

- AMVUTTRA is contraindicated in patients with a history of severe hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

- AMVUTTRA should be administered by a healthcare professional.
- Treatment should be started as early as possible in the disease course to prevent the accumulation of disability.
- Follow administration instructions carefully (see 4.4 Administration).
- There is limited experience with switching patients from other transthyretin (TTR) reducing agents; when switching, monitoring is recommended.
- The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.

4.2. Recommended Dose and Dosage Adjustment

Adults: The recommended dose of AMVUTTRA is 25 mg administered via subcutaneous injection once every 3 months.

Pediatric: Health Canada has not authorized an indication for pediatric use.

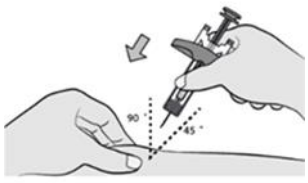
Geriatrics: No dose adjustment is required in patients 65 years of age or older (see 10.3 Pharmacokinetics).

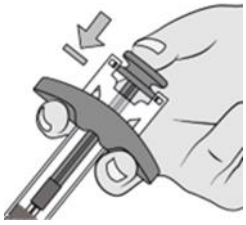
Hepatic Insufficiency: There is limited experience with the use of AMVUTTRA in patients with hepatic insufficiency. Based on population PK analyses, no dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ 1 x the upper limit of normal (ULN) and aspartate aminotransferase (AST) > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST) (see 10.3 Pharmacokinetics). AMVUTTRA has not been studied in patients with moderate or severe hepatic impairment.

Renal Insufficiency: There is limited experience with the use of AMVUTTRA in patients with renal insufficiency. Based on population PK analyses, 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) (see 10.3 Pharmacokinetics). AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

4.4. Administration

- AMVUTTRA should be administered by a healthcare professional.
- For subcutaneous use only.
- AMVUTTRA is supplied as a single-use prefilled syringe. Visually inspect the drug solution for particulate matter and discolouration. Do not use if discoloured or if particles are present.
- Prior to administration, if stored cold, allow AMVUTTRA to warm by leaving carton at room temperature for about 30 minutes.
- Administer subcutaneous injection into one of the following sites: the abdomen, thighs, or upper arms. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.
- If injecting into the abdomen, avoid the area around the navel.
- Clean the chosen injection site.
- Performing the injection:

1. 

2. 

3. 

1. Pinch the cleaned skin.
   Fully insert the needle into the pinched skin at a 45°-90° angle.
2. Inject all of the medication.
   Push the plunger rod as far as it will go to administer the dose and activate the needle shield.
3. Release the plunger rod to allow the needle shield to cover the needle.
   Do not block the plunger rod movement.
4. Immediately dispose of the used syringe into a sharps container.

4.5. Missed Dose

If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

5. Overdose

Reported experience with overdose is limited. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate treatment.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
subcutaneous injection	Solution; 25 mg / 0.5 mL (as vutrisiran sodium)	sodium chloride; sodium phosphate dibasic dihydrate; sodium phosphate monobasic dihydrate; water for injection. Phosphoric acid and sodium hydroxide may have been added to adjust pH.

AMVUTTRA contains vutrisiran, a chemically modified double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing three *N*-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

Description

AMVUTTRA contains 25 mg vutrisiran [equivalent to 26.5 mg vutrisiran sodium] in 0.5 mL per syringe. AMVUTTRA is a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous injection. AMVUTTRA is supplied as a 0.5-mL solution in a single-use, 1-mL prefilled syringe made from Type I glass with stainless steel 29-gauge needle with a needle shield. The prefilled syringe components are not made with natural rubber latex.

AMVUTTRA is available in cartons containing one single-use prefilled syringe.

7. Warnings and Precautions

General

- **Reduced Serum Vitamin A Levels and Recommended Supplementation**

By reducing serum transthyretin (TTR) protein, treatment with AMVUTTRA leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance/amount of vitamin A (3,000 IU/1,200 mcg RAE) is advised for patients taking AMVUTTRA. Serum vitamin A levels should not be used to guide vitamin A supplementation during treatment with AMVUTTRA (see 9.7 Drug-Laboratory Test Interactions and 10.2 Pharmacodynamics).

Driving and Operating Machinery

No studies with AMVUTTRA have been performed to assess effects on the ability to drive and operate machinery during treatment. AMVUTTRA is not expected to have significant influence on the ability to drive and use machines.

Monitoring and Laboratory Tests

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with AMVUTTRA 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, 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 during treatment with AMVUTTRA (see 7 Warnings and Precautions, General; 10.2 Pharmacodynamics).

Ophthalmologic

Ocular signs and symptoms may be caused by hATTR amyloidosis due to amyloid deposition in the eye. However, if a patient develops 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, referral to an ophthalmologist is recommended (see 7 Warnings and Precautions, General).

Reproductive Health

- **Fertility**

Treatment with AMVUTTRA reduces serum levels of vitamin A, which is thought to play an important role in fertility. There are no data on the effects of AMVUTTRA on human fertility. No impact on male or female fertility was detected in animal studies (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

- **Function**

There are no data on the effects of AMVUTTRA on human sexual function.

- **Teratogenic Risk**

Due to the potential teratogenic risk arising from unbalanced vitamin A levels, it is recommended that women of childbearing potential use effective contraception during treatment with AMVUTTRA. If a

woman intends to become pregnant, it is recommended to stop AMVUTTRA and monitor serum vitamin A levels. Serum vitamin A levels may remain reduced for more than 12 months after the last dose of AMVUTTRA.

In pregnant rats dosed daily during organogenesis, adverse reductions in fetal body weight were observed at greater than or equal to 10 mg/kg/day (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

7.1 Special Populations

7.1.1 Pregnancy

AMVUTTRA is not recommended for use during pregnancy (see 7 Warnings and Precautions, Reproductive health).

There are no data on the use of AMVUTTRA in pregnant women. The effects of a reduction in maternal serum TTR or serum vitamin A levels on the fetus are unknown (see 10.2 Pharmacodynamics).

During the first 60 days of pregnancy, too high or too low vitamin A levels may both be associated with an increased risk of fetal malformation. Therefore, pregnancy should be ruled out before initiating AMVUTTRA. Women of childbearing potential should practice effective contraception while receiving AMVUTTRA. If a woman intends to become pregnant, AMVUTTRA and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and seen to have returned to normal before conception is attempted.

In the event of an unplanned pregnancy, AMVUTTRA should be discontinued.

7.1.2. Breastfeeding

It is unknown if AMVUTTRA is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. There is no information regarding the presence of AMVUTTRA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMVUTTRA and any potential adverse effects on the breastfed infant from AMVUTTRA or from the underlying maternal condition.

There is no information on the effect of AMVUTTRA on vitamin A levels in human milk. Breast milk is a critical source of vitamin A for infants. Concentrations of vitamin A in breast milk may be influenced by the mother's vitamin A status (see 7 Warnings and Precautions, General).

7.1.3. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

7.1.4. Geriatrics

No overall differences in safety or effectiveness were observed between patients ≥ 65 years old and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8. Adverse Reactions

8.1. Adverse Reaction Overview

During the HELIOS-A 18-month treatment period, the most frequently occurring adverse reactions (≥10%) reported in patients treated with AMVUTTRA were pain in extremity (14.8%) and arthralgia (10.7%). None of the adverse reactions resulted in discontinuation of treatment.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Placebo-controlled study

In the Phase 3 randomized, open-label study (HELIOS-A), a total of 122 patients with hATTR amyloidosis received AMVUTTRA administered once every 3 months by subcutaneous injection. Of these, 118 patients received treatment for 18 months or more. The mean duration of treatment was 18.8 months (range: 1.7 to 19.4 months).

The safety profile of AMVUTTRA was generally consistent across all subgroups including age, sex, race, weight, geographic region, genotype, disease stage, and patients that met pre-defined criteria for cardiac involvement (baseline left ventricular [LV] wall thickness ≥ 13 mm with no history of hypertension or aortic valve disease).

Table 2– Adverse reactions reported in at least 5% of patients treated with AMVUTTRA and that occurred at least 3% more frequently than in patients treated with placebo*

	AMVUTTRA n=122 (%)	Placebo* n=77 (%)
Musculoskeletal and connective tissue disorders		
Pain in extremity	15	10
Arthralgia	11	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea†	7	0

*External placebo group from APOLLO randomized, controlled trial in patients with hATTR amyloidosis (Phase 3 trial with patisiran). Mean duration of exposure was 15 months (range: 1.3 to 18.8 months).

†Includes dyspnea, dyspnea exertional, and dyspnea paroxysmal nocturnal

8.3. Less Common Clinical Trial Adverse Reactions

Injection-site reactions

During the HELIOS-A 18-month treatment period, injection-site reactions were reported in 5 (4.1%) patients treated with AMVUTTRA, occurring in 0.6% of injections. Reported symptoms included

bruising, erythema, pain, pruritus, and warmth. Injection-site reactions were mild, transient, and did not lead to treatment discontinuation.

Immunogenicity

In the HELIOS-A study, 4 (3.3%) patients treated with AMVUTTRA developed anti-drug antibodies (ADA). ADA titers were low and transient with no evidence of an effect on clinical efficacy, safety, pharmacokinetic or pharmacodynamic profiles of vutrisiran.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the study described above with the incidence of antibodies in other studies or to other products may be misleading.

Other Less Common Adverse Reactions

Patient numbers were too low to accurately identify other less common adverse reactions (see 14.1 Clinical Trials by Indication).

9. Drug Interactions

9.2 Drug Interactions Overview

No formal clinical drug interaction studies have been performed with AMVUTTRA.

9.3 Drug-Behaviour Interactions

No formal studies on drug-behavioural interactions have been performed with AMVUTTRA.

9.4 Drug-Drug Interactions

No clinical studies on drug-drug interaction have been performed. AMVUTTRA is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes, or to modulate the activity of drug transporters.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with AMVUTTRA 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, 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 during treatment with AMVUTTRA (see 7 Warnings and Precautions, General; 10.1 Mechanism of Action).

10. Clinical Pharmacology

10.1 Mechanism of Action

In patients with hATTR amyloidosis, variant and wild-type serum TTR proteins form amyloid deposits in tissues, leading to progressive polyneuropathy and cardiomyopathy.

Vutrisiran is a chemically modified double-stranded siRNA that specifically targets variant and wild-type *TTR* messenger RNA (mRNA), and is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable targeted delivery of the siRNA to hepatocytes.

Through a natural process called RNA interference (RNAi), vutrisiran causes the catalytic degradation of *TTR* mRNA in the liver, resulting in a reduction of serum TTR protein and a consequent reduction of amyloid deposits in tissues.

10.2 Pharmacodynamics

In the Phase 3 HELIOS-A study, the pharmacodynamic effects of 25 mg AMVUTTRA administered subcutaneously once every 3 months were evaluated in patients with hATTR amyloidosis. Mean serum TTR was reduced by 64% from baseline as early as Day 22, with near steady-state TTR reduction of 73% by Week 6. With repeat dosing every 3 months, mean reductions of serum TTR after 9 and 18 months of treatment were 83% and 88%, respectively. Similar TTR reductions were observed regardless of genotype (V30M or non-V30M), prior TTR stabilizer use, weight, sex, age, or race. The median percent reduction in serum TTR levels in the vutrisiran arm was non-inferior to the within-study patisiran reference arm through Month 18, with a difference of 5.3% (95% CI; 1.2, 9.3) (see 14.1 Clinical Trials by Indication).

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. In patients taking concomitant vitamin A supplements, AMVUTTRA decreased vitamin A levels with mean steady state peak and trough reductions of 70% and 63%, respectively (see 7 Warnings and Precautions, General; 9.7 Drug-Laboratory Test Interactions).

Cardiac electrophysiology

Vutrisiran had no effect on QTc interval in healthy subjects who received doses up to 300 mg. A dedicated thorough QT study has not been conducted with vutrisiran.

10.3 Pharmacokinetics

The pharmacokinetic properties of AMVUTTRA were characterized by measuring the plasma and urine concentrations of vutrisiran.

Table 3 - Summary of vutrisiran pharmacokinetic parameters in patients with hATTR amyloidosis

	C_{max} (mcg/mL)	T_{max} (hours)	$AUC_{0-\infty}$ (h·mcg/mL)
Single dose mean (SD)	N=120 0.1138 (0.0936)	N=120 3.12* (2.0, 6.6)	N=20 0.79 (0.31)†

*T_{max} reported as median (minimum, maximum)

†For a majority of the patients, vutrisiran plasma concentrations reached the lower limit of quantitation (LLOQ) by 24 hours and as a result, AUC_{0-24} could only be estimated for few patients.

Absorption

Following subcutaneous administration, vutrisiran is rapidly absorbed with a time to maximum plasma concentration (t_{max}) of 3.0 (range: 2.0 to 6.5) hours. At the recommended dosing regimen of 25 mg once every 3 months subcutaneously, the mean (% coefficient of variation [%CV]) steady state peak concentrations (C_{max}), and area under the concentration time curve from 0 to 24 hours (AUC_{0-24}) were 0.12 mcg/mL (64.3%), and 0.80 mcg·h/mL (35.0%), respectively. There was no accumulation of vutrisiran in plasma after repeated quarterly dosing.

Distribution

Vutrisiran is greater than 80% bound to plasma proteins over the concentration range observed in humans at the dose of 25 mg once every 3 months subcutaneously. Vutrisiran plasma protein binding was concentration-dependent and decreased with increasing vutrisiran concentrations (from 78% at 0.5 mcg/mL to 19% at 50 mcg/mL). The population estimate for the apparent central compartment volume of distribution (V_d/F) of vutrisiran in humans was 10.2 L (% Relative standard error [RSE]=5.71%). Vutrisiran distributes primarily to the liver after subcutaneous dosing.

There are no clinical data on the PK of vutrisiran in the liver. In animal studies, liver C_{max} after single subcutaneous injections were reached by 7 and 24 h in rats and monkeys, respectively. Targeted delivery of vutrisiran to the liver was confirmed by consistently higher concentrations in liver compared with plasma in both rats and monkeys. After a single subcutaneous dose to rats (0.3 to 3 mg/kg) and to monkeys (0.3 to 30 mg/kg), liver AUC_{last} was 4350- to 11,425-fold higher than plasma exposure across the range of doses tested in rats and 2600- to 21,000-fold in monkeys. The $t_{½}$ of vutrisiran, in liver, after a single dose was 3.5 to 6.3 days in rats and 18 to 31 days in monkeys across the range of doses tested.

Metabolism

Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver. There were no major circulating metabolites in humans. In vitro studies indicate that vutrisiran does not undergo metabolism by CYP450 enzymes.

Elimination

Following a 25-mg single subcutaneous dose, the median apparent plasma clearance was 21.4 (range: 19.8, 30.0) L/h. The median terminal elimination half-life ($t_{1/2}$) of vutrisiran was 5.23 (range: 2.24, 6.36) hours. After a single subcutaneous dose of 5 to 300 mg, the mean fraction of unchanged drug

eliminated in urine ranged from 15.4% to 25.4% and the mean renal clearance ranged from 4.45 to 5.74 L/h for vutrisiran.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of AMVUTTRA have not been studied in children or adolescents < 18 years old; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).
- **Geriatrics:** In the open-label HELIOS-A study, 46 (38%) patients treated with AMVUTTRA were ≥ 65 years old and of these, 7 (5.7%) patients were ≥ 75 years old. There were no significant differences in steady-state pharmacokinetic parameters or TTR reduction between patients < 65 years old and ≥ 65 years old.
- **Sex:** Clinical studies did not identify clinically significant differences in steady state vutrisiran pharmacokinetic parameters or TTR reduction based on sex.
- **Pregnancy and breastfeeding:** Vutrisiran has not been studied in pregnant and breastfeeding women.
- **Genetic polymorphism:** Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver. Based on the in vitro data, vutrisiran is not a substrate, inhibitor, or inducer of CYP enzymes or transporters. Vutrisiran is not expected to be affected by genetic polymorphisms in CYP enzymes or transporters.
- **Ethnic origin:** Clinical studies did not identify clinically significant differences in steady-state vutrisiran pharmacokinetic parameters or TTR reduction based on race.
- **Hepatic Insufficiency:** Population pharmacokinetic and pharmacodynamic analyses indicated no impact of mild hepatic impairment (total bilirubin ≤ 1 x ULN and AST > 1 x ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST) on AMVUTTRA exposure or TTR reduction compared to patients with normal hepatic function. AMVUTTRA has not been studied in patients with moderate or severe hepatic impairment.
- **Renal Insufficiency:** 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 AMVUTTRA exposure or TTR reduction compared to subjects with normal renal function. AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

11. Storage, Stability, and Disposal

Store at 2 °C to 30 °C in the original carton, until ready for use.

Do not freeze.

Part 2: Scientific Information

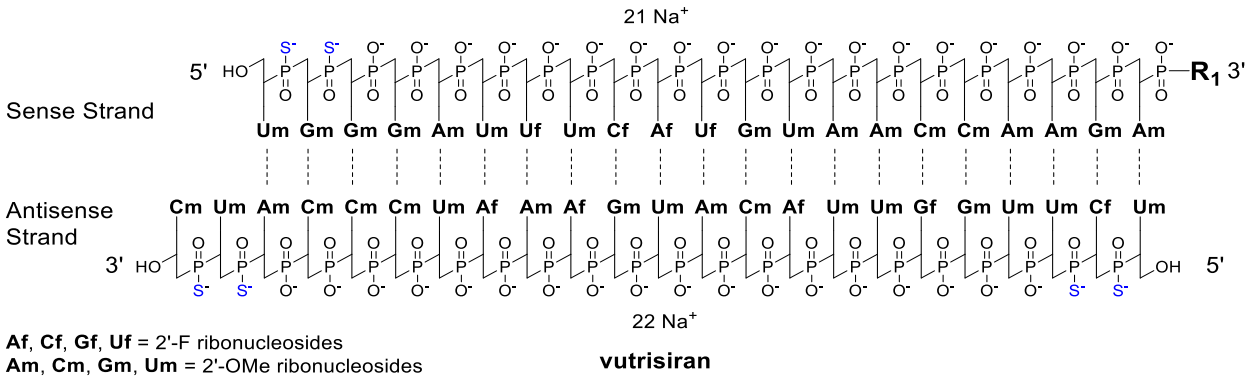
13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: vutrisiran sodium

Molecular formula and molecular mass: C_{530} H_{672} F_9 N_{171} Na_{43} O_{323} P_{43} S_6; 17290 Da.

Structural formula:



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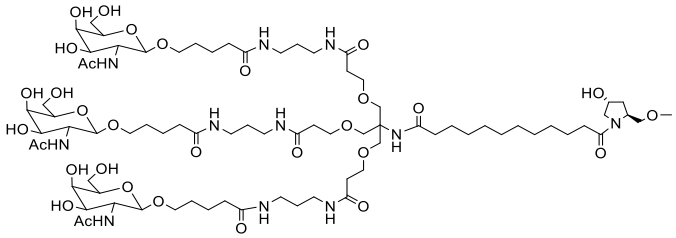


Physicochemical properties:

- The solubility of vutrisiran drug substance in water has been determined to be 361 mg/mL
- pH of a 1% solution in KCl: approximately 7.0

14 Clinical Trials

14.1 Clinical Trials by Indication

Indication: Treatment of Polyneuropathy in Adult Patients with hATTR Amyloidosis

Table 4 - Summary of Patient Demographics for Clinical Trial in Patients with hATTR Amyloidosis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age Years (Range)	Sex
ALN-TTRSC02-002 (HELIOS-A)	Global, randomized (3:1), open-label	25 mg, via subcutaneous injection, once every 3 months, for 18 months	vutrisiran: 122 patisiran: 42	58 (26, 85)	Male (65%) Female (35%)

The efficacy of AMVUTTRA was demonstrated in a global, randomized, open-label clinical trial (HELIOS-A) in adult patients with hATTR amyloidosis with stage 1 or stage 2 polyneuropathy. Patients were randomized 3:1 to receive 25 mg of AMVUTTRA (N=122) subcutaneously once every 3 months, or 0.3 mg/kg patisiran (N=42) intravenously every 3 weeks as a reference group.

The treatment period of the study was conducted over 18 months with analyses performed at Month 9 and Month 18. Ninety-seven percent (97%) and ninety-six percent (96%) of patients treated with AMVUTTRA completed at least 9 and 18 months of the assigned treatment, respectively. Efficacy assessments were based on a comparison of the vutrisiran arm of the study with an external placebo group (placebo arm of the APOLLO Phase 3 study) comprised of a similar population of patients with hATTR amyloidosis with polyneuropathy. All Month 9 endpoints were analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 endpoints were analyzed using the mixed-effects model for repeated measures (MMRM).

Of the patients who received AMVUTTRA, the median patient age at baseline was 60 years and 65% of patients were male. Seventy percent (70%) of patients were Caucasian, 17% were Asian, 3% were Black, and 9% were reported as Other. Patients were from Western Europe (35%), North America (22%), or rest of world (43%). Twenty-two (22) different transthyretin (TTR) variants were represented: V30M (44%), T60A (13%), E89Q (8%), A97S (6%), S50R (4%), V122I (3%), L58H (3%), and Other (18%). Twenty percent (20%) of patients had the V30M genotype and early onset of symptoms (< 50 years old). At baseline, 69% of patients had stage 1 disease (unimpaired ambulation; mild sensory, motor and autonomic neuropathy in the lower limbs), and 31% had stage 2 disease (assistance with ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk). Sixty-one percent (61%) of patients had prior treatment with TTR stabilizers. According to the New York Heart Association (NYHA) classification of heart failure, 9% of patients had class I and 35% had class II. Thirty-three percent (33%) of patients met pre-defined criteria for cardiac involvement (baseline LV wall thickness ≥ 13 mm with no history of hypertension or aortic valve disease).

Month 9 assessments

The primary efficacy endpoint was the change from baseline to Month 9 in modified Neuropathy

Impairment Score +7 (mNIS+7). This endpoint is a composite measure of motor, sensory, and autonomic neuropathy, including assessments of motor strength, 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.

The clinical meaningfulness of effects on the mNIS+7 was assessed by the key secondary endpoint, which was the change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN questionnaire is a patient-reported assessment that includes domains relating to small fiber, large fiber, and autonomic nerve function, symptoms of polyneuropathy, and activities of daily living, with the total score ranging from -4 to 136, where increasing score indicates worsening quality of life. Secondary efficacy endpoints at 9 months also included gait speed (10-meter walk test).

Month 18 assessments

Efficacy assessments included a change from baseline to Month 18 for mNIS+7, Norfolk QoL-DN, 10-meter walk test, nutritional status (modified body mass index [mBMI]), and patient-reported ability to perform activities of daily living and social participation such as eating, bathing, dressing, and standing (Rasch-Built Overall Disability Scale [R-ODS]).

Study Results

Table 5 - Results of Study ALN-TTRSC02-002 in Patients with hATTR Amyloidosis

Endpoint	**Baseline, Mean (SD)**		**Change from Baseline, LS Mean (SEM)**		**AMVUTTRA-Placebo[†] Treatment Difference, LS Mean (95% CI)**	***p*-value**
	AMVUTTRA N=122	**Placebo[†] N=77**	**AMVUTTRA**	**Placebo[†]**		
Month 9						
mNIS+7[‡] *(Primary Endpoint)*	60.6 (36.0)	74.6 (37.0)	-2.2 (1.4)	14.8 (2.0)	-17.0 (-21.8, -12.2)	$p < 0.0001$
Norfolk QoL-DN[‡]	47.1 (26.3)	55.5 (24.3)	-3.3 (1.7)	12.9 (2.2)	-16.2 (-21.7, -10.8)	$p < 0.0001$
Month 18						
mNIS+7[‡]	60.6 (36.0)	74.6 (37.0)	-0.5 (1.6)	28.1 (2.3)	-28.6 (-34.0, -23.1)	$p < 0.0001$
Norfolk QoL-DN[‡]	47.1 (26.3)	55.5 (24.3)	-1.2 (1.8)	19.8 (2.6)	-21.0 (-27.1, -14.9)	$p < 0.0001$
mBMI[¶]	1057.5 (233.8)	989.9 (214.2)	25.0 (9.5)	-115.7 (13.4)	140.7 (108.4, 172.9)	$p < 0.0001$

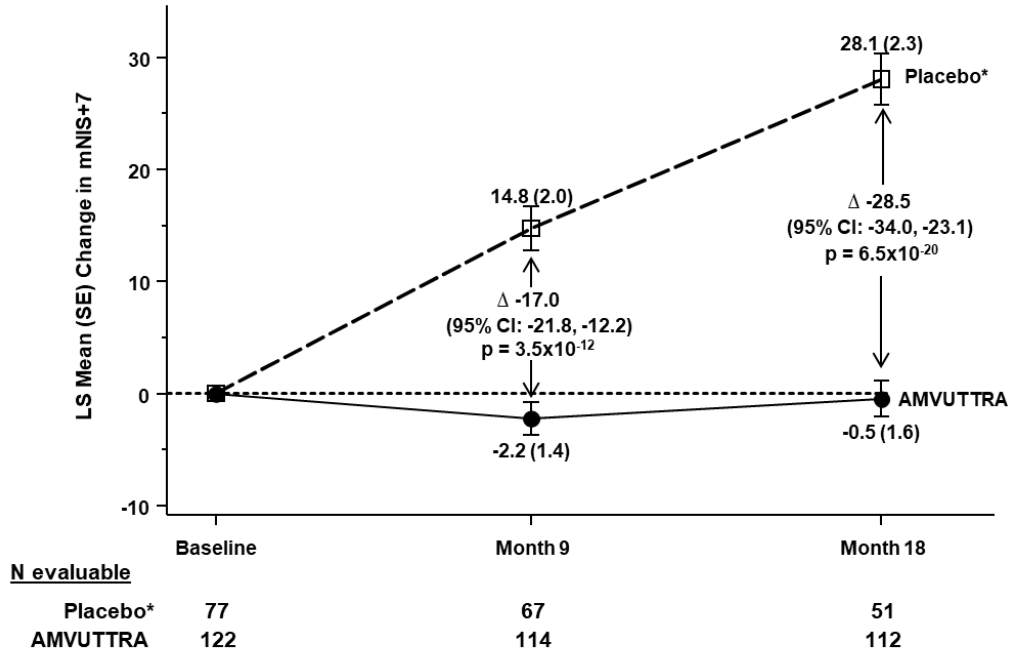
Abbreviations: CI = confidence interval; LS mean = least squares mean; mBMI = modified body mass index; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life - Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean;
[†]External placebo group from APOLLO randomized controlled trial.
[‡]A lower number indicates less impairment/fewer symptoms.
[¶]mBMI: body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

Treatment with AMVUTTRA led to an improvement in mNIS+7, relative to placebo ($p < 0.0001$) at 9 months (primary endpoint) and 18 months (Table 5 and Figure 1).

A statistically significant benefit in favor of AMVUTTRA treatment was also demonstrated for Norfork QoL-DN change from baseline to Month 9 and Month 18 (Table 5).

Treatment with AMVUTTRA in the HELIOS-A study also demonstrated statistically significant improvements in all other secondary endpoints measured from baseline to Month 9 or Month 18, compared to the external placebo group (all $p < 0.0001$).

Figure 1 - Change from Baseline in mNIS+7 (Month 9 and Month 18)



N evaluable			
Placebo*	77	67	51
AMVUTTRA	122	114	112

A decrease in mNIS+7 indicates improvement.
Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA – placebo.
*External placebo group from APOLLO randomized controlled trial.

Patients receiving AMVUTTRA experienced similar improvements relative to those in the placebo group in mNIS+7 and Norfolk QoL-DN total score at Month 9 and Month 18 across all subgroups including age, sex, race, region, NIS score, V30M genotype status, prior TTR stabilizer use, disease stage (1 and 2), and patients that met pre-defined criteria for cardiac involvement.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General toxicology: Vutrisiran is pharmacologically active in monkeys but not in rodents or rabbits.

In studies performed in monkeys, there were no observed effects of vutrisiran on the cardiovascular, respiratory, or central nervous systems, with a no observed effect level (NOEL) of 300 mg/kg (the highest dose evaluated).

Following once monthly repeated dosing for up to 6 months in rats and 9 months in monkeys, the mild and consistent non-adverse histological changes in liver (hepatocytes, Kupffer cells), kidneys (renal tubules), lymph nodes and injection sites (macrophages) reflected the principal distribution and accumulation of vutrisiran. However, no toxicities were identified at up to more than 1 000- and 3 000-fold higher plasma AUC, when normalised to quarterly dosing and compared to the anticipated exposure at the maximum recommended human dose [MRHD].

Serum samples taken from rats as part of the long-term toxicity study were negative for the presence of anti-drug antibodies. In monkeys, 8/32 animals had a positive anti-drug antibody response with low titers; baseline (predose) positivity was observed in 3 animals, suggesting the presence of pre-existing cross-reactive antibodies. There were no effects of anti-drug antibodies on pharmacodynamics, toxicokinetics or toxicity of vutrisiran.

Genotoxicity: Vutrisiran was not mutagenic in the bacterial reverse mutation assay, clastogenic or aneugenic in the chromosome aberration assay in human blood peripheral lymphocytes, and did not induce micronucleus formation in rat bone marrow following subcutaneous administration.

Carcinogenicity: In a 2-year carcinogenicity study in Sprague Dawley rats, no related neoplastic or proliferative findings were noted at the highest dose levels tested (15 mg/kg [once monthly] or 15 mg/kg [once every 3 months] in males, and 25 mg/kg [once monthly] or 25 mg/kg [once every 3 months] in females). When normalized to the once every 3 months clinical dosing schedule, the AUC-based exposure margins at 15 mg/kg (once monthly) and at 25 mg/kg (once monthly) for male and female rats, respectively, are 57 times and 52 times the human exposure at the maximum recommended human dose.

In a 2-year carcinogenicity study in CD-1 mice, vutrisiran was not carcinogenic at the highest dose tested in males (13 mg/kg [once monthly]). When normalized to the once every 3 months clinical dosing schedule, the AUC-based exposure margin at 13 mg/kg (once monthly) for male mice is 26x the human exposure at the MRHD. In female mice dosed once monthly with vutrisiran at 3, 9, or 18 mg/kg, a statistically significant dose-dependent trend for combined hepatocellular adenomas and carcinomas was observed. Given the absence of these findings in males and the lack of preneoplastic lesions in the liver of females, the clinical relevance of these findings in female mice is unclear.

Reproductive and developmental toxicology: Vutrisiran is not pharmacologically active in rats and rabbits, which limits the predictivity of these investigations. Once weekly doses of a rat-specific orthologue of vutrisiran did not impact fertility and early embryonic development in female rats. However, the impact of vutrisiran-induced TTR and vitamin A reduction could not be assessed using this model.

Weekly subcutaneous administrations of vutrisiran did not affect fertility and early embryonic development at more than 300-times the normalised MRHD. In an embryo-foetal study with daily subcutaneous vutrisiran administration in pregnant rats, adverse effects on maternal body weight, food consumption, increased premature delivery and post-implantation loss were observed with a maternal NOAEL of 10 mg/kg/day that was more than 300-times the normalised MRHD of 0.005 mg/kg/day. Based on an adverse reduction in fetal body weights and increased skeletal variations at ≥10 mg/kg/day, the fetal NOAEL of vutrisiran was 3 mg/kg/day which is 97-times the normalised MRHD.

In an embryo-fetal development study in pregnant rabbits, vutrisiran was administered subcutaneously at doses of 0, 3, 10, or 30 mg/kg/day during organogenesis (GD 7-19). No adverse effects on embryo-fetal development were observed at ≤ 30 mg/kg which is 1935 times the normalized MRHD.

In a prenatal-postnatal development study, vutrisiran was administered subcutaneously to pregnant female rats on GD 7, 13, 19 and on lactation days 6, 12, and 18 at doses of 0, 5, 10, or 20 mg/kg. There was no effect on growth and development of the offspring at ≤ 20 mg/kg.

Juvenile toxicity: No studies have been conducted.

Special toxicology: In monkeys receiving a vitamin A replete diet, repeated once monthly subcutaneous doses of vutrisiran at 1 and 3 mg/kg resulted in > 95% maximum reductions in serum TTR protein concentrations. Repeated once-monthly subcutaneous administration of vutrisiran at ≥ 30 mg/kg resulted in the expected sustained reductions from baseline in circulating TTR (up to 99%) without any apparent toxicological findings. A secondary effect on serum vitamin A concentrations resulted in decreases (up to 89%). These reductions were not associated with signs of vitamin A deficiency, as evaluated through ophthalmic examinations, electroretinograms, and histopathology of the eye. However, these findings may be confounded by the vitamin A replete diet, the impact of which remains unclear. Similarly, a secondary effect on thyroxine (decreases up to 48%) was observed, with no effect on histopathology of the thyroid.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AMVUTTRA®

vutrisiran injection

This Patient Medication Information is written for the person who will be taking **AMVUTTRA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **AMVUTTRA,** talk to a healthcare professional.

What AMVUTTRA is used for:

AMVUTTRA is used to treat stage 1 or 2 polyneuropathy (damage to peripheral nerves) in adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis).

How AMVUTTRA works:

hATTR amyloidosis is caused by problems with a protein in the body called 'transthyretin' (TTR). AMVUTTRA works by lowering the amount of TTR protein in the body. This can help to reduce the symptoms of hATTR amyloidosis.

The ingredients in AMVUTTRA are:

Medicinal ingredient: vutrisiran (as vutrisiran sodium)

Non-medicinal ingredients: sodium chloride, sodium phosphate dibasic dihydrate, sodium phosphate monobasic dihydrate, water for injections. Sodium hydroxide and phosphoric acid may be used to adjust the pH.

AMVUTTRA comes in the following dosage forms:

Solution for injection: 25 mg/0.5 mL

Do not use AMVUTTRA if:

- You have ever had a severe allergic reaction to vutrisiran, or any of the other ingredients of this medicine. If you are not sure, talk to your healthcare professional before you are given AMVUTTRA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AMVUTTRA. Talk about any health conditions or problems you may have.

Other warnings you should know about:

Lowered vitamin A levels in the blood and vitamin A supplements: Treatment with AMVUTTRA lowers the amount of vitamin A in your blood. Your healthcare professional will ask you to take a vitamin A supplement every day. Your healthcare professional will tell you the dose of vitamin A that is right for you. Signs of low vitamin A may include:

- sight problems especially at night,
- dry eyes,
- poor vision,
- hazy or cloudy vision.

If you notice a change in your vision or any other eye problems while on AMVUTTRA, talk to your healthcare professional. Your healthcare professional may send you to an eye specialist for a check-up.

Fertility: AMVUTTRA lowers the amount of vitamin A in your blood, which may have an effect on fertility. Talk to your healthcare professional if this is a concern for you.

Pregnancy and birth control: Before starting treatment with AMVUTTRA, tell your healthcare professional if you are pregnant, think you may be pregnant or are planning on becoming pregnant. Your healthcare professional may have you take a pregnancy test before starting treatment with AMVUTTRA. You should not take AMVUTTRA if you are pregnant. AMVUTTRA affects your levels of vitamin A, and low or high levels of vitamin A may harm the baby. If you become pregnant while being treated with AMVUTTRA, tell your healthcare professional **right away**.

If you are able to become pregnant, you should use effective birth control while taking AMVUTTRA. Talk to your healthcare professional about suitable methods of birth control.

Breastfeeding: Before starting treatment with AMVUTTRA, tell your healthcare professional if you are breastfeeding or are planning to breastfeed. You and your healthcare professional should decide if the benefit of breastfeeding is greater than the risk to your baby. This is because this medicine may pass into the breast milk, and it is not known how it will affect the baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AMVUTTRA:

Interactions with other drugs are not known.

How AMVUTTRA is given:

- AMVUTTRA will be given to you by a healthcare professional.
- AMVUTTRA is given as an injection under the skin (subcutaneous injection) into your stomach area (abdomen), your upper arm or thigh.

Usual dose:

The usual dose of AMVUTTRA is 25 mg once every 3 months.

Overdose:

This medicine will be given to you by a healthcare professional. In the unlikely event that you are given too much (an overdose) your healthcare professional will check you for side effects.

If you think you, or a person you are caring for, have been given too much AMVUTTRA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss an appointment for your AMVUTTRA injection, contact your healthcare professional as soon as you can to arrange to have the injection you missed.

Possible side effects from using AMVUTTRA :

These are not all the possible side effects you may have when taking AMVUTTRA. If you experience any side effects not listed here, tell your healthcare professional.

Very common side effects include:

- Pain in the joints (arthralgia)
- Pain in the arms, hands, feet, and legs

Common side effects include:

- Shortness of breath (dyspnea)
- Redness, pain, itching, bruising, or warmth where the injection was given (injection site reaction)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at 2 °C to 30 °C in the original carton, until ready for use. Do not freeze.
- Keep out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

If you want more information about AMVUTTRA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.alnylam.ca) or by calling 1-877-256-9526.

This leaflet was prepared by Alnylam Netherlands B.V.

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