swissmedic

Date: 23 April 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Amvuttra

International non-proprietary name: vutrisiran sodium

Pharmaceutical form: solution for injection in pre-filled syringe

Dosage strength(s): the usual recommended dose of Amvuttra is 25 mg administered via subcutaneous injection once every 3 months.

Route(s) of administration: subcutaneous use, single use only

Marketing authorisation holder: Alnylam Switzerland GmbH

Marketing authorisation no.: 69074

Decision and decision date: approved on 23.06.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for vutrisiran sodium in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 17 October 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication
Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy

2.2.2 Approved indication
Amvuttra 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
The recommended dose of Amvuttra is 25 mg administered via subcutaneous injection once every 3 months.

2.2.4 Approved dosage
(see appendix)

2.3 Regulatory history (milestones)

Application	1 November 2022
Formal control completed	21 November 2022
List of Questions (LoQ)	21 March 2023
Response to LoQ	12 April 2023
Preliminary decision	6 June 2023
Response to preliminary decision	23 June 2023
Final decision	23 June 2023
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Amvuttra - EMA/CHMP/689555/2022 (12.10.2022) issued by the EMA.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The quality aspects in this SwissPAR refer to the publicly available assessment report Amvuttra - EMA/CHMP/689555/2022, published 12.10.2022, issued by the EMA.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Amvuttra - EMA/CHMP/689555/2022, published 12.10.2022, issued by the EMA.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Amvuttra - EMA/CHMP/689555/2022, published 12.10.2022, issued by the EMA

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Amvuttra 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

AMVUTTRA®, solution for injection in pre-filled syringe

Composition

Active substances

Vutrisiran (as vutrisiran sodium). It contains synthetically produced, chemically modified small interfering ribonucleic acid (siRNA).

Excipients

Sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, water for injection, sodium hydroxide (for pH adjustment), phosphoric acid (for pH adjustment), contains 5.9 mg of sodium per 1 mL.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe. Subcutaneous use. Single use only.
Appearance
Clear, colourless-to-yellow solution (pH of approximately 7; osmolality 210 to 390 mOsm/kg).
Quantity of active substance per unit
Each pre-filled syringe contains 25 mg vutrisiran (as vutrisiran sodium) in 0,5 mL of solution (50mg / mL).

Indications/Uses

Amvuttra 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 under the supervision of a physician knowledgeable in the management of amyloidosis. Treatment should be started as early as possible in the disease course to prevent the accumulation of disability.
Usual dosage
The recommended dose of Amvuttra is 25 mg administered via subcutaneous injection once every 3 months.
Vitamin A supplementation at approximately, but not exceeding, 2500 IU to 3000 IU vitamin A per day is advised for patients treated with Amvuttra (see section «Warnings and Precautions»).

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.

Patients with hepatic disorders

No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ 1 x 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). Vutrisiran has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section «*Pharmacokinetics»*).

Patients with renal disorders

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). Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section «*Pharmacokinetics»*).

Elderly patients

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

Children and adolescents

The safety and efficacy of Amvuttra in children or adolescents < 18 years of age have not been established. No data are available.

Delayed administration

If a dose is missed, Amvuttra should be administered as soon as possible. Dosing should be resumed every 3 months, from the most recently administered dose.

Mode of administration

Amvuttra is for subcutaneous use only. Amvuttra should be administered by a healthcare professional. This medicinal product is ready-to-use and for single-use only.
Visually inspect the solution for particulate matter and discolouration. Do not use if discoloured or if particles are present.
Prior to administration, if stored cold, the pre-filled syringe should be allowed to warm by leaving carton at room temperature for about 30 minutes.

- The subcutaneous injection should be administered into one of the following sites: the abdomen, thighs, or upper arms. Amvuttra should not be injected into scar tissue or areas that are reddened, inflamed, or swollen.
- If injecting into the abdomen, the area around the navel should be avoided.

Contraindications

Severe hypersensitivity (e.g., anaphylaxis) to the active substance or to any of the excipients listed in section «*Composition»*.

Warnings and precautions

Vitamin A deficiency
By reducing serum transthyretin (TTR) protein, Amvuttra treatment leads to a decrease in serum vitamin A (retinol) levels (see «Properties/Effects»). Serum vitamin A levels below the lower limit of normal should be corrected and any ocular symptoms or signs due to vitamin A deficiency should be evaluated prior to initiation of treatment with Amvuttra.

Patients receiving Amvuttra should take oral supplementation of approximately, but not exceeding, 2500 IU to 3000 IU vitamin A per day to reduce the potential risk of ocular symptoms due to vitamin A deficiency. 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.

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 Amvuttra and women of childbearing potential should practise effective contraception (see «Pregnancy, lactation»). If a woman intends to become pregnant, Amvuttra and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted. Serum vitamin A levels may remain reduced for more than 12 months after the last dose of Amvuttra.

In the event of an unplanned pregnancy, Amvuttra should be discontinued (see «Pregnancy/ lactation»). No recommendation can be given whether to continue or discontinue vitamin A supplementation during the first trimester of an unplanned pregnancy. If vitamin A supplementation is continued, the daily dose should not exceed 3000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 2500 IU to 3000 IU per day should be resumed in the second and third trimesters if serum vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

It is not known whether vitamin A supplementation in pregnancy will be sufficient to prevent vitamin A deficiency if the pregnant female continues to receive Amvuttra. However, increasing vitamin A supplementation to above 3000 IU per day during pregnancy is unlikely to correct plasma retinol levels due to the mechanism of action of Amvuttra and may be harmful to the mother and foetus.

Other ingredients

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

Interactions

No clinical interaction studies have been performed. Vutrisiran is not expected to cause interactions or to be affected by inhibitors or inducers of cytochrome P450 enzymes, or to modulate the activity of transporters. Therefore, vutrisiran is not expected to have clinically significant interactions with other medicinal products.

Pregnancy, lactation

Women of child-bearing age

Treatment with Amvuttra 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 initiation of treatment and women of childbearing potential should use effective contraception. If a woman intends to become pregnant, Amvuttra and vitamin A supplementation should be discontinued and serum vitamin A levels should be monitored and have returned to normal before conception is attempted (see section «*Warnings and Precautions*»). Serum vitamin A levels may remain reduced for more than 12 months after the last dose of treatment.

Pregnancy

There are no data on the use of Amvuttra in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section «*Preclinical Data*»). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Amvuttra should not be used during pregnancy. As a precautionary measure, vitamin A (see section «*Warnings and Precautions*») and TSH (thyroid stimulating hormone) levels should be obtained early in pregnancy. Close monitoring of the foetus should be carried out, especially during the first trimester.

Lactation

It is unknown whether vutrisiran is excreted in human milk. There is insufficient information on the excretion of vutrisiran in animal milk (see section «*Preclinical Data*»).
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Amvuttra, 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 Amvuttra on human fertility. No impact on male or female fertility was detected in animal studies (see section «*Preclinical Data*»).

Effects on ability to drive and use machines

Amvuttra has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

During the HELIOS-A 18-month treatment period, the most frequently occurring adverse reactions reported in Amvuttra-treated patients were pain in extremity (15%) and arthralgia (11%).

List of adverse reactions

The adverse reactions are presented as MedDRA preferred terms and under the MedDRA System Organ Class (SOC). The frequency of the adverse reactions is expressed according to the following categories:

- "very common" (≥1/10)
- "common" (≥1/100, <1/10),
- "uncommon" (≥1/1,000, <1/100)

Table 1: Adverse reactions reported for Amvuttra

System Organ Class	Adverse reaction	Frequency
Respiratory, thoracic, and mediastinal disorders	Dyspnoea[a]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Pain in extremity	Very common
General disorders and administration site conditions	Injection site reaction[b]	Common
Investigations	Blood alkaline phosphatase increased	Common
[a] Includes dyspnoea, dyspnoea exertional and dyspnoea paroxysmal nocturnal [b] Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild, transient, and did not lead to treatment discontinuation		

Description of specific adverse reactions and additional information

Immunogenicity

During the HELIOS-A 18-month treatment period, 4 (3.3%) Amvuttra-treated patients developed anti-drug antibodies (ADA). ADA titres were low and transient with no evidence of an effect on clinical efficacy, safety, or pharmacokinetic or pharmacodynamic profiles of vutrisiran.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, it is recommended that the patient be monitored as medically indicated for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

Properties/Effects

ATC code

N07XX18

Mechanism of action

Amvuttra contains vutrisiran, a chemically stabilized double-stranded small interfering ribonucleic acid (siRNA) that specifically targets variant and wild-type transthyretin *(TTR)* messenger RNA (mRNA) and is covalently linked to a ligand containing three *N* - acetylgalactosamine (GalNAc) residues to enable 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 the reduction of variant and wild-type serum TTR protein levels.

Pharmacodynamics

Mean serum TTR was reduced as early as Day 22, with mean near to steady state TTR reduction of 73% by Week 6. With repeat dosing of 25 mg once 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 stabiliser use, weight, sex, age, or race.
Serum TTR is a carrier of retinol binding protein 4, which is the principal carrier of vitamin A in the blood. Amvuttra decreased vitamin A levels with mean steady state peak and trough reductions of 70% and 63%, respectively (see sections «*Warnings and Precautions*» and «*Interactions*»).

Clinical efficacy

The efficacy of Amvuttra was studied in a global, randomised, open-label clinical study (HELIOS-A) in adult patients with hATTR amyloidosis with polyneuropathy. Patients were randomised 3:1 to receive 25 mg of Amvuttra (N=122) subcutaneously once every 3 months, or 0.3 mg/kg patisiran (N=42) intravenously once every 3 weeks. The treatment period of the study was conducted over 18 months with two analyses at Month 9 and at Month 18. Ninety-seven percent (97%) of Amvuttra-treated patients completed at least 18 months of the assigned treatments (vutrisiran or patisiran). 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. Assessment of non-inferiority of serum TTR reduction was based on comparison of the vutrisiran arm to the within-study patisiran arm.

Of the patients who received Amvuttra, the median patient age at baseline was 60 years (range 34 to 80 years), 38% were ≥ 65 years old, and 65% of patients were male. Twenty-two (22) different 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). There were no patients with stage 3 disease. Sixty-one percent (61%) of patients had prior treatment with TTR tetramer stabilisers. 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).

The primary efficacy endpoint was the change from baseline to Month 18 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 change from baseline to Month 18 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score was assessed as a secondary endpoint. The Norfolk QoL-DN questionnaire (patient-reported) includes domains relating to small fibre, large fibre, 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.

Other secondary endpoints included gait speed (10-meter walk test), nutritional status (mBMI), and patient-reported ability to perform activities of daily living and social participation (Rasch-Built Overall Disability Scale [R-ODS]).

Treatment with Amvuttra in the HELIOS-A study demonstrated statistically significant improvements in all endpoints (Table 2 and Figure 1) measured from baseline to Month 9 and 18, compared to the external placebo group of the APOLLO study (all $p < 0.0001$).

The time-averaged trough TTR percent reduction through Month 18 was 84.7% for vutrisiran and 80.6% for patisiran. The percent reduction in serum TTR levels in the vutrisiran arm was non-inferior (according to predefined criteria) to the within-study patisiran arm through Month 18 with a median difference of 5.3% (95% CI 1.2%, 9.3%).

Table 2: Summary of clinical efficacy results from the HELIOS-A study

Endpoint[a]	Baseline, Mean (SD)		Change from Baseline, LS Mean (SEM)		Amvuttra -Placebo[b] Treatment Difference, LS Mean (95% CI)	*p*-value
	Amvuttra N=122	Placebo[b] **N=77**	Amvuttra	Placebo[b]		
Month 9						
mNIS+7[c]	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[c]	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
10-meter walk test (m/sec)[d]	1.01 (0.39)	0.79 (0.32)	0 (0.02)	-0.13 (0.03)	0.13 (0.07, 0.19)	*p*<0.0001
Month 18						
mNIS+7[c]	60.6 (36.0)	74.6 (37.0)	-0.5 (1.6)	28.1 (2.3)	-28.5 (-34.0, -23.1)	*p*<0.0001
Norfolk QoL-DN[c]	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
10-meter walk test (m/sec)[d]	1.01 (0.39)	0.79 (0.32)	-0.02 (0.03)	-0.26 (0.04)	0.24 (0.15, 0.33)	*p*<0.0001
mBMI[e]	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
R-ODS[f]	34.1 (11.0)	29.8 (10.8)	-1.5 (0.6)	-9.9 (0.8)	8.4 (6.5, 10.4)	*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

[a] All Month 9 endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analyzed using the mixed-effects model for repeated measures (MMRM)

[b] External placebo group from APOLLO randomised controlled study

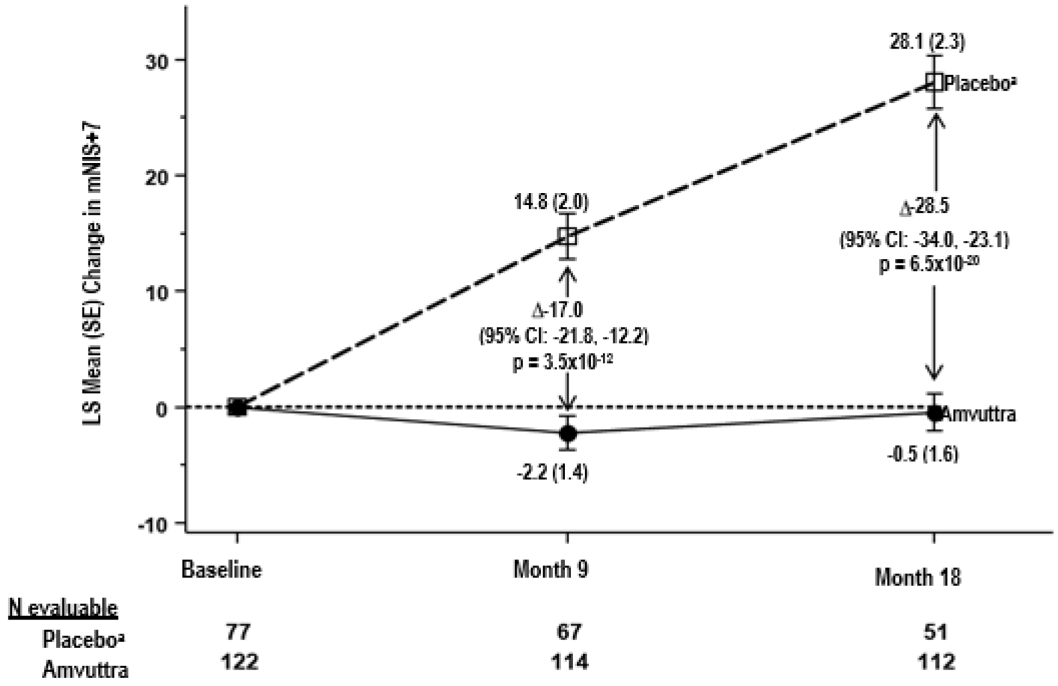
[c] A lower number indicates less impairment/fewer symptoms

[d] A higher number indicates less disability/less impairment

[e] mBMI: body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L); a higher number indicates better nutritional status.

[f] A higher number indicates less disability/less impairment.

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



A decrease in mNIS+7 indicates improvement

Δ indicates between-group treatment difference, shown as the LS mean difference (95% CI) for AMVUTTRA –external placebo

All Month 9 endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method and all Month 18 analyzed using the mixed-effects model for repeated measures (MMRM)

[a] External placebo group from APOLLO randomised controlled study

Patients receiving Amvuttra experienced similar benefit relative to placebo 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 stabiliser use, disease stage, and patients with or without pre-defined criteria for cardiac involvement.

The N-terminal prohormone-B-type natriuretic peptide (NT-proBNP) is a prognostic biomarker of cardiac dysfunction. NT-proBNP baseline values (geometric mean) were 273 ng/L and 531 ng/L in Amvuttra-treated and placebo-treated patients, respectively. At Month 18, the geometric mean NT-proBNP levels decreased by 6% in Amvuttra patients, while there was a 96% increase in placebo patients.

Centrally-assessed echocardiograms showed changes in LV wall thickness (LS mean difference: -0.18 mm [95% CI -0.74, 0.38]) and longitudinal strain (LS mean difference: -0.4% [95% CI -1.2, 0.4]) with Amvuttra treatment relative to placebo.

Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed.

Paediatrics

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

Pharmacokinetics

The pharmacokinetic properties of Amvuttra were characterised by measuring the plasma and urine concentrations of vutrisiran.

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 µg/mL (64.3%), and 0.80 µg·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 µg/mL to 19% at 50 µg/mL). The population estimate for the apparent central compartment volume of distribution (Vd/F) of vutrisiran in humans was 10.2 L (% Relative standard error [RSE]=5.71%). Vutrisiran distributes primarily to the liver after subcutaneous dosing.

Metabolism

Vutrisiran is metabolised by endo- and exo-nucleases 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 active substance 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.

Linearity/non-linearity

Following single subcutaneous doses over the 5 to 300 mg dose range, vutrisiran C_{max} was shown to be dose proportional while area under the concentration-time curve from the time of dosing extrapolated to infinity (AUC_{inf}) and area under the concentration-time curve from the time of dosing to the last measurable concentration (AUC_{last}) were slightly more than dose proportional.

Pharmacokinetic/pharmacodynamic relationship(s)

Population pharmacokinetic/pharmacodynamic analyses in healthy subjects and patients with hATTR amyloidosis (n=202) showed a dose-dependent relationship between predicted vutrisiran liver concentrations and reductions in serum TTR. The model-predicted median steady state peak, trough, and average TTR reductions were 88%, 86%, and 87%, respectively, confirming minimal peak-to-trough variability across the 3-month dosing interval. Covariate analysis indicated similar TTR reduction in patients with mild-to-moderate renal impairment or mild hepatic impairment, as well as by sex, race, prior use of TTR stabilisers, genotype (V30M or non-V30M), age and weight.

Kinetics in specific 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.

Hepatic impairment

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 vutrisiran exposure or TTR reduction compared to patients with normal hepatic function. Vutrisiran 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 vutrisiran exposure or TTR reduction compared to subjects with normal renal function. Vutrisiran has not been studied in patients with severe renal impairment or end-stage renal disease.

Elderly patients

In the HELIOS-A study, 46 (38%) patients treated with vutrisiran 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.

Preclinical data

Repeated once-monthly subcutaneous administration of vutrisiran at ≥ 30 mg/kg in monkeys produced the expected sustained reductions of circulating TTR (up to 99%) and vitamin A (up to 89%) without any apparent toxicological findings.
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 1000- and 3000-fold higher plasma AUC, when normalised to quarterly dosing and compared to the anticipated exposure at the maximum recommended human dose [MRHD].

Genotoxicity and Carcinogenicity

Vutrisiran did not exert any genotoxic potential *in vitro* and *in vivo*. Carcinogenicity studies have not been completed.

Reproductive toxicity

Vutrisiran is not pharmacologically active in rats and rabbits, which limits the predictivity of these investigations. Nevertheless, a single dose of a rat-specific orthologue of vutrisiran did not impact on fertility and early embryonic development in a combined study in rats.

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 foetal body weights and increased skeletal variations at ≥10 mg/kg/day, the foetal NOAEL of vutrisiran was 3 mg/kg/day which is 97-times the normalised MRHD.

In an embryo-foetal development study in pregnant rabbits, no adverse effects on embryo-foetal development were observed at ≤ 30 mg/kg/day vutrisiran, which is more than 1900-times the normalised MRHD.

In a prenatal-postnatal development study, subcutaneous vutrisiran administration on every 6th day had no effect on growth and development of the offspring with a NOAEL of 20 mg/kg, which was more than 90-times the normalised MRHD.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C. Do not freeze.
Keep out of the reach of children.

Instructions for handling

Please refer to the Annex.

Authorisation number

69074

Packs

AMVUTTRA® 25 mg, solution for injection in pre-filled syringe (Type I glass) with stainless steel 29-gauge needle with a needle shield.
Each pack contains 1 pre-filled syringe [B].

Marketing authorisation holder

Alnylam Switzerland GmbH, Zug

Date of revision of the text

May 2023

ANNEX: Instructions for use

Amvuttra 25 mg solution for injection in pre-filled syringe

vutrisiran

Healthcare professionals should refer to the Healthcare Professional Information for full prescribing information.

Posology and method of administration

Therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis.

Posology

The recommended dose is 25 mg vutrisiran administered by subcutaneous injection once every 3 months.

Missed dose

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

Method of administration

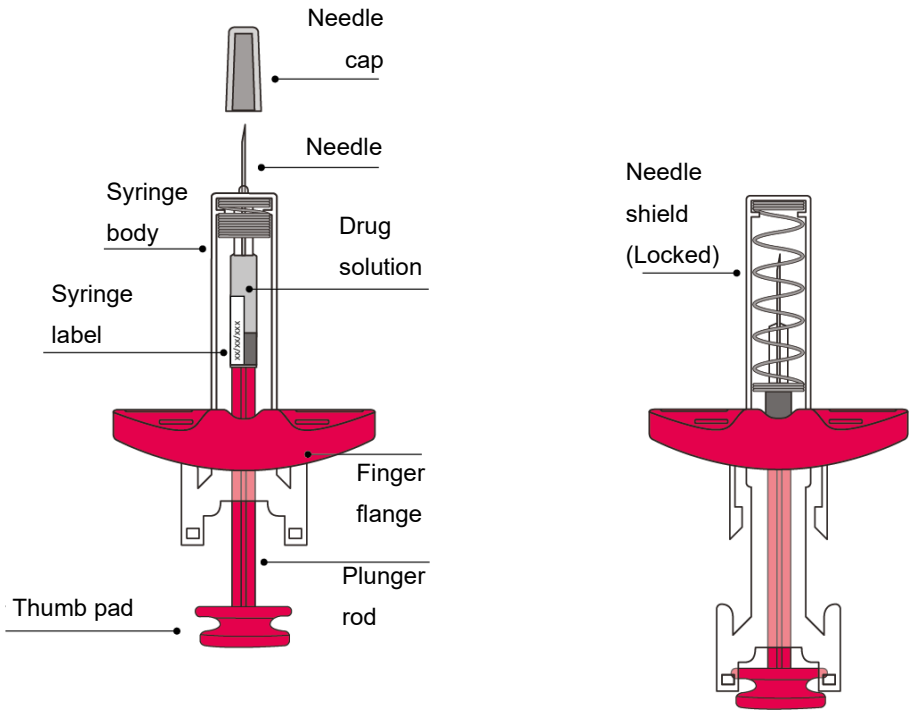
Amvuttra is for subcutaneous use only and should be administered by a healthcare professional.

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.
- Each 25 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single-use only.

How the syringe looks before and after use:

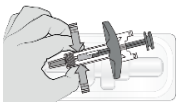
Before Use **After Use**



1. Prepare syringe

   If the syringe has been stored cold prior to use, allow the syringe to warm to room temperature for 30 minutes prior to use.

   Remove the syringe from the packaging by gripping the syringe body.



   Do not touch plunger rod until ready to inject.

   Amvuttra is a sterile, preservative-free, clear, colourless-to-yellow solution. Visually inspect the solution. **Do not** use if it contains particulate matter or if it is cloudy or discoloured.

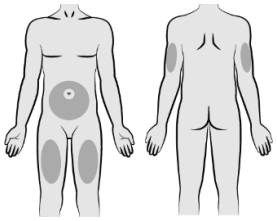
   Check:

   - Syringe is not damaged, such as cracked or leaking
   - Needle cap is attached to the syringe
   - Expiry date on syringe label.

   Do not use the syringe if any issues are found while checking the syringe.

2. Choose injection site

Choose an injection site from the following areas: the abdomen, thighs, or upper arms.



Avoid:

- Area around the navel
- Scar tissue or areas that are reddened, inflamed, or swollen.

Clean the chosen injection site.

3. Prepare for injection

Hold the syringe body with one hand. Pull the needle cap straight off with other hand and dispose of needle cap immediately. It is normal to see a drop of liquid at the tip of the needle.

Do not touch the needle or let it touch any surface.

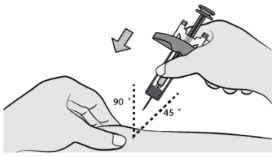
Do not recap the syringe.

Do not use the syringe if it is dropped.

4. Perform Injection

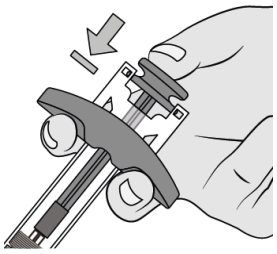
Pinch the cleaned skin.

Fully insert the needle into the pinched skin at a 45-90° angle.

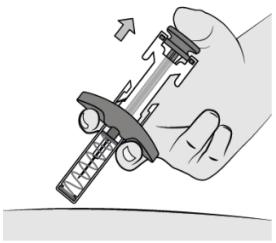


Inject all of the medicine

Push the plunger rod as far as it will go to administer the dose and activate the needle shield.



Release the plunger rod to allow the needle shield to cover the needle.



Do not block plunger rod movement.

5. Dispose of syringe

Immediately dispose of the used syringe into a sharps container.