Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Amvuttra 25 mg solution for injection in pre-filled syringe

(vutrisiran sodium)

PLGB 50597/0006

Alnylam Netherlands B.V.

LAY SUMMARY

Amvuttra 25 mg solution for injection in pre-filled syringe (vutrisiran sodium)

This is a summary of the Public Assessment Report (PAR) for Amvuttra. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Amvuttra in this lay summary for ease of reading.

For practical information about using Amvuttra, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Amvuttra and what is it used for?
This product has been authorised by MHRA for Great Britain (GB; consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 16 September 2022 (EMEA/H/C/005852/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

Amvuttra is used in adults only for the treatment of an illness called 'hereditary ATTR' or 'hATTR amyloidosis'. This is an illness which runs in families. hATTR amyloidosis is caused by problems with a protein in the body called 'transthyretin' (TTR). This protein is made mostly in the liver and carries vitamin A and other substances around the body.

In people with this illness, small fibres of TTR protein clump together to make deposits called 'amyloid'. Amyloid can build up around or within the nerves, heart, and other places in the body, stopping them from working normally. This causes the symptoms of the illness.

How does Amvuttra work?
The active substance in Amvuttra, vutrisiran (as vutrisiran sodium), works by lowering the amount of TTR protein made by the liver which means there is less TTR protein in the blood that can form amyloid. This can help to reduce the effects of this illness.

How is Amvuttra used?
The pharmaceutical form of this medicine is a solution for injection in pre-filled syringe.

This medicine will be given to patient by a doctor, pharmacist, or nurse.

How much Amvuttra is the patient given
The recommended dose is 25 mg once every 3 months.

Where the injection is given
Amvuttra is given by injection under the skin ('subcutaneous injection') into the stomach area (abdomen), upper arm or thigh.

How long to use Amvuttra
The patient's doctor will tell the patient how long they need to receive Amvuttra. The patient should not stop treatment with Amvuttra unless their doctor tells them to.

For further information on how Amvuttra is used, refer to the PIL and Summary of Product

Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Amvuttra have been shown in studies?
In one main study involving 164 patients with hATTR amyloidosis with stage 1 or 2 nerve damage, Amvuttra was shown effective at slowing down the nerve damage caused by the disease.

The main measure of effectiveness was the change in the patients' nerve damage, as measured by a standard scale called 'mNIS+7', where a decreased score indicates an improvement and an increased score indicates worsening nerve damage. After 18 months of treatment, the mNIS+7 score decreased on average by around 0.5 points with Amvuttra. This was compared with an average increase of 28 points seen with placebo (a dummy treatment) in another study involving 225 patients comparing Onpattro (another hATTR amyloidosis medicine) with placebo.

The study also showed that treatment with Amvuttra was at least as effective as Onpattro at reducing transthyretin levels.

What are the possible side effects of Amvuttra?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Amvuttra approved?
Amvuttra was shown to be effective at slowing down nerve damage in patients with hATTR amyloidosis with stage 1 or stage 2 nerve damage. Regarding safety, the side effects are considered manageable.

The MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Amvuttra has been authorised with the condition to perform further studies to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Amvuttra?"

Amvuttra has been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Amvuttra?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Amvuttra. The RMP details the important risks of Amvuttra, how these risks can be minimised, any uncertainties about Amvuttra (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Amvuttra:

Summary of safety concerns	
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

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Amvuttra are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Amvuttra product information, the Marketing Authorisation Holder (MAH) has committed to additional pharmacovigilance activities through the provision of safety data derived from ongoing and follow-up studies.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Amvuttra
A Marketing Authorisation was granted in Great Britain on 16 September 2022.

The full PAR for Amvuttra follows this summary.

This summary was last updated in November 2022.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Amvuttra 25 mg solution for injection in pre-filled syringe (PLGB 50597/0006) could be approved.

The product is approved for the following indication:

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

Amvuttra contains the active substance, vutrisiran (as vutrisiran sodium), 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.

This product has been authorised by MHRA for Great Britain (GB; consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 16 September 2022 (EMEA/H/C/005852/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

This application was evaluated for fulfilment of orphan designation criteria. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan approval.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (EMEA-002425-PIP01-18).

At the time of the submission of the application the PIP was completed.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a full product specific waiver (P/0015/2019).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing Authorisation was granted in GB on 16 September 2022.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

IV. NON-CLINICAL ASPECTS

The MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

V. CLINICAL ASPECTS

The MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risk:		
Clinical consequences of vitamin A deficiency, including delayed symptoms	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	Routine PV activities beyond adverse reactions reporting and signal detection: • Specific targeted follow-up of vitamin A deficiency/ocular toxicity Additional PV activities: • Evaluation of data from the HELIOS-A Randomised Treatment Extension (HELIOS-A RTE) • Evaluation of data from the ConTTRibute Study
Hypersensitivity Reactions	Routine risk minimisation measures: • SmPC Section 4.3 and PIL Section 2 • Legal status: Prescription-only Additional risk minimisation measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A Randomised Treatment Extension (HELIOS-A RTE)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		• Evaluation of data from the ConTTRibute Study
Missing Information:		
Longer-term safety (>2 years)	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the HELIOS-A Randomised Treatment Extension (HELIOS-A RTE) • Evaluation of data from the ConTTRibute Study
Use in patients with moderate or severe hepatic impairment	Routine risk minimisation measures: • SmPC sections 4.2 and 5.2 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the ConTTRibute Study
Use in pregnant women and effects on pregnancy outcomes	Routine risk minimisation measures: • SmPC sections 4.4, 4.6, and 5.3, and PIL Section 2 Additional risk minimisation measures: • None	Routine PV activities beyond adverse reactions reporting and signal detection: • None Additional PV activities: • Evaluation of data from the ConTTRibute Study

Abbreviations: PIL=Patient Information Leaflet; PV=Pharmacovigilance; RTE=Randomised Treatment Extension; SmPC=Summary of Product Characteristics.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

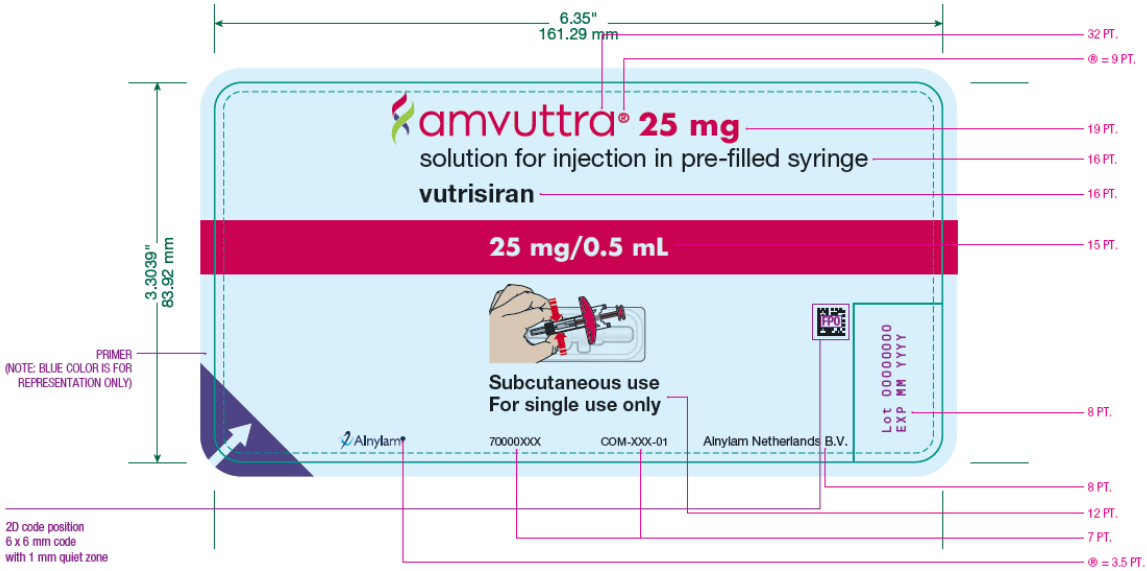
Amvuttra 25 mg solution for injection in pre-filled syringe has been authorised with the condition to perform further studies to minimise the risk. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

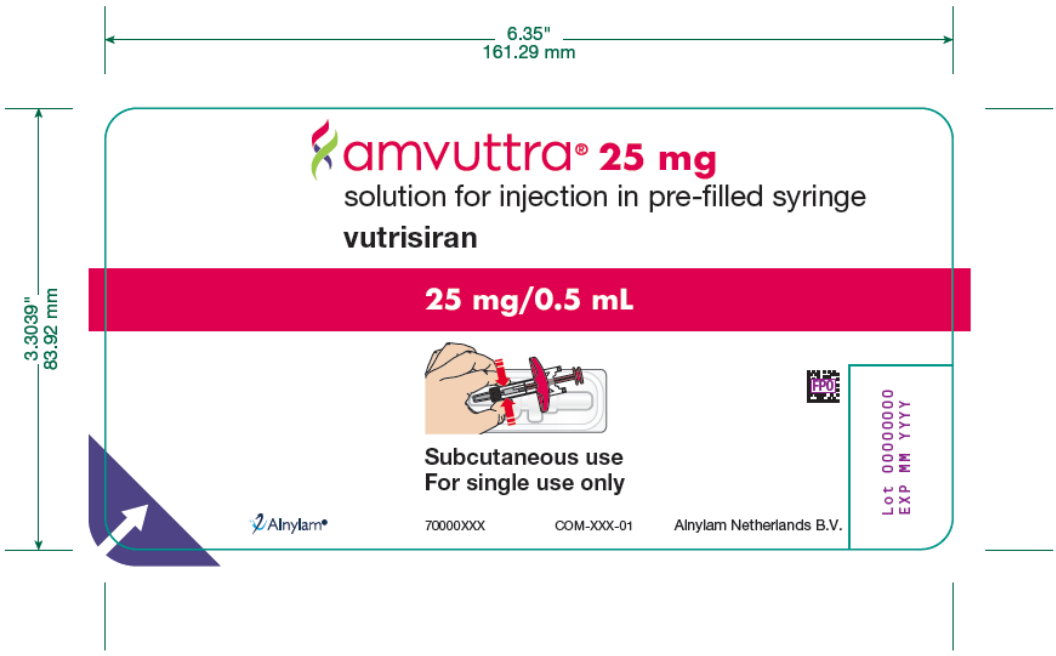
Description	**Due date**
1.PASS Category 3 ALN-TTRSC02-002 HELIOS-A-RTE study is a Phase 3 global, randomised, open-[1]label study to evaluate the safety and efficacy of ALN[1]TTRSC02 in patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis). The aim of the study is to collect further longer-term safety and efficacy data on vutrisiran in patients with hATTR amyloidosis with polyneuropathy.	31/12/2025
2. The active substance specification limits for duplex purity, purity and impurities including specified impurities by denaturing AX-HPLC UV as well as IPRP-UPLC UV, melting temperature, sodium content, assay, pH and water content should be re-assessed when there are available data from an additional 10 batches manufactured with the commercial process.	31/12/2027
3. Submission of the reports from carcinogenicity studies in rats and mice	31/03/2024
4. The finished product specification limits for purity and impurities should be reassessed when there are available data from an additional 10 batches manufactured with the commercial process.	31/12/2027
5. PASS Category 3 ALN-TTR02-013 ConTTRibute Study: A global prospective observational multicenter long-term study of patients with hATTR amyloidosis. The primary objective of this study is to document the natural history, clinical characteristics, and management of ATTR amyloidosis as part of routine clinical care. This study is enrolling hATTR and wtATTR amyloidosis patients and was initiated in November 2020. Long- term safety data for vutrisiran will be collected as part of ConTTRibute.	31/12/2034

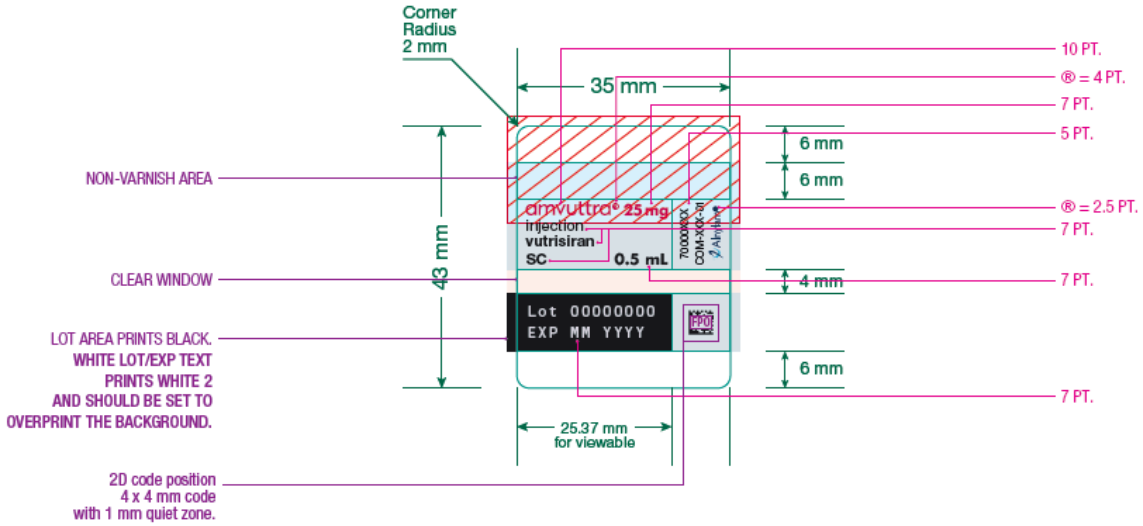
The SmPC, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved GB version of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of GB licensing are provided below.






Corner Radius 2 mm
35 mm
10 PT.
® = 4 PT.
7 PT.
5 PT.
6 mm
6 mm
NON-VARNISH AREA
® = 2.5 PT.
7 PT.
43 mm
CLEAR WINDOW
4 mm
7 PT.
Lot 00000000
EXP MM YYYY
LOT AREA PRINTS BLACK.
WHITE LOT/EXP TEXT
PRINTS WHITE 2
AND SHOULD BE SET TO
OVERPRINT THE BACKGROUND.
6 mm
7 PT.
25.37 mm
for viewable
2D code position
4 x 4 mm code
with 1 mm quiet zone.

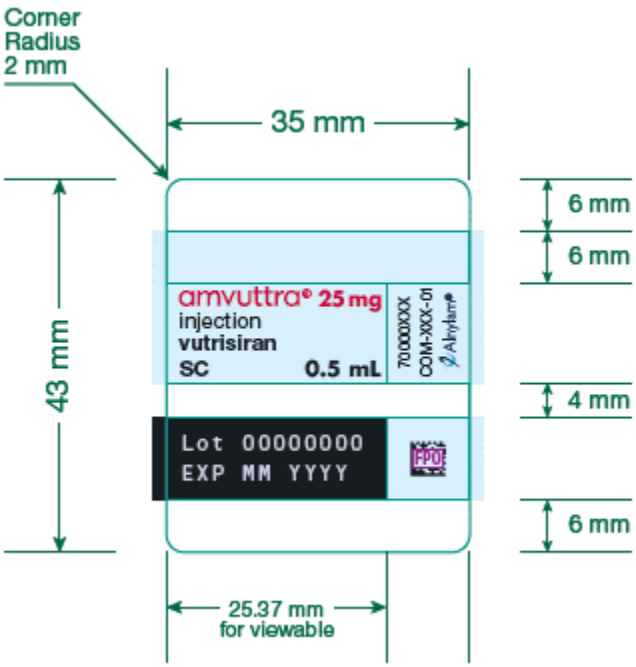

Corner Radius 2 mm
35 mm
6 mm
6 mm
43 mm
amvuttra® 25 mg
injection
vutrisiran
SC 0.5 mL
4 mm
Lot 00000000
EXP MM YYYY
6 mm
25.37 mm
for viewable

TABLE OF CONTENTS OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the Marketing Authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Product: Amvuttra 25 mg solution for injection in pre-filled syringe
Active substance: Vutrisiran
Orphan Designation Number: PLGB 50597/0006/OD1

Background:

This application was evaluated for fulfilment of orphan designation criteria and the designation criteria were considered fulfilled.

Evaluation:

Orphan condition
The orphan condition is transthyretin-mediated amyloidosis (ATTR amyloidosis). This is acceptable and in line with the guidance on what constitutes a valid condition.

Orphan indication
The orphan indication is the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

Life threatening/ debilitating condition
Transthyretin (TTR)-mediated amyloidosis (ATTR amyloidosis) is a rare, serious, life-threatening, multi-systemic disease encompassing hereditary ATTR amyloidosis (hATTR amyloidosis) and wild-type ATTR amyloidosis (wtATTR amyloidosis), which results from either hereditary (genetic variant) or non-hereditary causes, respectively. In ATTR amyloidosis, misfolded TTR protein deposits as amyloid fibrils and plaques in tissues of various organs, resulting in progressive, chronically debilitating morbidity and mortality. The most common manifestations of ATTR amyloidosis are cardiomyopathy and polyneuropathy

The constellation of progressive morbidity from amyloid infiltration in patients with hATTR amyloidosis results in severe disability, wasting due to gastrointestinal malabsorption, malnutrition, and cardiac cachexia. Death can result from heart failure (including sudden death caused by ventricular arrhythmias or electromechanical dissociation) or infection. It is reported that the median survival is 4.7 years following diagnosis with a reduced survival (3.4 years) for patients presenting with cardiomyopathy. Similarly, it has been reported that in patients with wild-type ATTR (wtATTR) amyloidosis, median survival from diagnosis is 3.5 to 4 years and the most common cause of death is heart failure and sudden death.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects an estimated 1.1 to 2.9 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of diagnosis/prevention/ treatment
The treatment of hATTR amyloidosis requires a multidisciplinary approach primarily involving neurology, cardiology, and gastroenterology specialties.

There are currently three MHRA-approved therapies available in Great Britain for the treatment of hATTR amyloidosis in adults with polyneuropathy: ONPATTRO (patisiran, an RNAi therapeutic), TEGSEDI (inotersen, an antisense oligonucleotide [ASO]) and Vyndaqel (tafamidis, a TTR tetramer stabilizer).

Patisiran and inotersen act by targeting the production of transthyretin (TTR) synthesis in the liver by acting on mRNA; patisiran through RNAi and inotersen through RNAse H-mediated cleavage. Tafamidis acts by binding to the thyroxine-binding site on TTR to reduce its dissociation into misfolded amyloidogenic monomers.

Other treatment approaches currently used in clinical practice for hATTR amyloidosis include: orthotopic liver transplantation (OLT), which eliminates variant TTR from the circulation, and diflunisal, another TTR tetramer stabilizer (not approved for this indication in any country).

OLT is primarily effective in patients with an early age of onset (<50 years of age) and those with the V30M variant and short disease duration before liver transplant. Thus, OLT remains a treatment option only for a small subgroup of hATTR amyloidosis patients.

Justification of significant benefit
Significant benefit of vutrisiran over tafamidis has been demonstrated. While tafamidis is indicated in the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy, vutrisiran has a broader indication in the treatment of transthyretin amyloidosis in adult patients with stage 1 and 2 polyneuropathy.

Significant benefit of vutrisiran over inotersen has been demonstrated based on a major contribution to patient care (less frequent administration, every 3 months compared to weekly injection of inotersen) and supported by a better safety profile with no need for the frequent laboratory monitoring of platelet counts and renal function that is required for inotersen and demonstrated efficacy in patients with moderate or severe renal impairment (a contraindication for treatment with inotersen). From the indirect comparison it appears that the efficacy of vutrisiran is at least non inferior to inotersen.

Significant benefit of vutrisiran over patisiran has been demonstrated based on major contribution to patient care (subcutaneous injection every 3 months instead of patisiran intravenous infusions every 3 weeks) supported by patient-rated convenience of the dosing schedule. It appears efficacy of vutrisiran is at least non inferior to patisiran.

OLT is primarily effective in patients with an early age of onset (<50 years of age) and those with the V30M variant and short disease duration before liver transplant. Thus, OLT remains a treatment option only for a small subgroup of hATTR amyloidosis patients.

In summary, in light of the evidence of a substantial benefit on patients with a range of disease manifestations, and encouraging and manageable safety, vutrisiran has a favourable benefit-risk profile for the treatment of hATTR amyloidosis in adult patients with polyneuropathy, and offers clear, clinically relevant advantages over existing treatments thus satisfying the criterion of significant benefit for obtaining an Orphan Drug Designation in Great Britain.

Conclusion:

Conclusion on acceptability of orphan designation
The applicant has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 16 September 2022